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CHAIRPERSON'S MESSAGE

The world is undergoing a massive churning. The worldwide outbreak of novel corona virus has brought the global economy on its knees. More than 12 million people have been infected and death count has crossed half a million mark. Though it started in China, China was quick to put all out efforts to control it within Hubei province through strict lockdown measures, comprehensive testing, isolation, arrangement of emergency hospital beds with ventilators and integrated treatment through applying both, modern medicine and traditional Chinese medicine(TCM).

The pandemic arrived in India in late spring and it was anticipated that with the warmer summer, its spread would stall. Indian government took timely measure of a prolonged national lockdown. But, once the lockdown has started getting lifted gradually, the virus has spread in several pockets of the country. We may be reaching the figure of a million infection within a week.

The trade-off between lockdown and flow of economy has complex dynamics. Similarly, the prolonged lockdown has affected the mode of education. While video tutorials were only supplements to the classroom teaching, now online classes have become new normal. Webinar and Zoom Classes are getting popular with the institutions for cost-cutting and also being adopted by students for the comfort that these offer.

In a post-pandemic world, what would be the optimal mix of virtual and real classrooms is something that needs to be pondered by our educationists, psychologists and cognitive neuroscientists. Will adoption of 5-G technology make virtual classes more exciting with augmented reality? Or will there be demand for "Back to Classroom," politicizing the new generation of children? These are some of the challenges during coming times which require serious attention of our researchers.

In the current issue, we are carrying two papers on Covid pandemic and we hope to publish many more in coming issues!

I wish the whole team involved with the complex task of bringing out a journal in these trying times for their perseverance and dedication.

Dr. Ashok Kumar Gadiya
Chairperson,
Mewar University

Covid pandemic has put a question mark over our understanding about nature. Though, mankind is better equipped to understand the etiology of the disease with array of sophisticated instruments for observation, we are still not able to find out a cure against Covid infection. Three vaccines have entered third phase of clinical trial and likely to take few more months before the same is available in the market. In the meantime, alternative knowledge tradition continues to spring surprises with handy treatment. On 17th March, Wu Dong, Professor at the Peking Union Medical College Hospital along with China's top three Doctors addressed media in Beijing and claimed efficacy of Traditional Chinese Medicine (TCM). In Wuhan, among 87% of patients with mild disease of Corona infection, TCM worked quite well and also in those who have recovered from their critical illness.

The herbs used in China are root of *Radix astragali* (Huang qi黄(耆), roots of *Radix glycyrrhizae* (Gan cao 甘草), roots of *Radix saposhnikoviae* (Fang feng 防风), *Rhizoma atractylodis Macrocephalae* (Bai 白朮), flower of *Lonicerae japonicae flos* (Jin yin hua 金銀花), and fruit of *Fructus forsythia* (Lian qiao 连).

Buoyed by the efficacy of traditional medicine, Ministry of AYUSH in India came up with right combination of traditional medicine as preventive measure and immunity booster for mass usage. The AYUSH Ministry has also proposed to Indian Council of Medical research(ICMR) for conducting trial of some Ayurvedic medicine on COVID-19 patients. In the meantime, AYUSH Ministry has advised drinking of herbal tea / decoction (*Kadha*) made from Tulsi (Basil, Botanical name: *Ocimum basilicum*), Dalchini (Cinnamon, Botanical name: *Cinnamomum verum*), Kalimirch (Black pepper, Botanical name: *Piper nigrum*), Shunthi (Dry Ginger, Botanical name: *Zingiber officinale*) and Munakka (Raisin), once or twice a day. Jaggery (natural sugar) and / or fresh lemon juice may be added as per taste.

Trikatu-Black pepper (*Piper nigrum*), Long pepper (*Piper longum*), Ginger (*Zingiber officinale*) itself has been a popular combination in Traditional Indian Medicine (TIM). It is used even now in clearing excess mucous from throat and lungs. Lemon gives vitamin C. Its combination is always helpful for clearing mucous from lung, which causes respiratory problem and ultimately choking of lungs in extreme cases. This is the major cause of mortality in Covid cases.

Kuth (*Saussurea costus*) is a native herbal plant found in Kashmir valley, Himachal Pradesh and Uttarakhand. It is also known as the snow lotus or costus root, and has been used in traditional medicine for long. Its roots have been traded for fragrance and efficacy for millennia. Kuth is used for various respiratory problems. In case of nasal infection one can take Kuth powder, Bael giri powder (*Aegle marmelos*), Pippali (*Piper longum*), Saunth (Dry Ginger), Munakka (grapes) and Til oil (Sesame oil). After processing it and filtration, it can be taken as nasal drops in common cold.

Kuth is also taken in asthma and bronchitis by mixing its powder with kulthi, kateri, saunth and certain aromatic grasses.

Then, we have Karkoti (*Momordica dioica*) which has anti-inflammatory, and hepato-protective property. Devadaali (*Luffa echinata*) is helpful in bronchitis, and jaundice. It is anti-inflammatory, analgesic and anti-oxidant. The bark of Kadamba (*Neolamarckia cadamba*) possess quinovic acid which has been found to have anti-viral property. Bark also has anti-inflammatory property which is a plus point in the COVID treatment to reduce inflammation. The leaves of the plant has anti-pyretic property and then also anti-diarrhea as well as anti-malarial property. In a way, it has several properties which are antidote to the various symptoms caused by the COVID-19.

We know how quinine was derived from cinchona tree found in Amazon forests. This has dramatically reduced global mortality by helping to eradicate malaria. Several other native Amazonian medicines of plant origin, particularly in Peru, are known to have anti-microbial and anti-inflammatory activity, anti-viral and immune-modulating effects. Some of the studied plants are : Sangre de Grado (drago) (*Croton lechleri*) in the Euphorbiaceae family and Una de Gato (*Uncaria tomentosa*) in the Rubiaceae family.

Uncaria tomentosa (Cat's claw) too has quinovic acid just like in the bark of the Kadamba tree. Quinovic acid induces immuno-stimulant activity and the plant is being harnessed for dengue virus treatment. Quinovic acid from *Uncaria tomentosa* has been found effective against two different RNA-virus, Vesicular Stomatitis virus, and Rhinovirus 1B*, in vitro.*

Since, COVID-19 too has been a RNA-Virus, which does respond to the Chloroquine *in vitro*, derived from bark of another Amazon plant, Cinchona(from same Andean region and Rubiaceae family to which Cat's claw belongs); an urgent trial of *in vitro* effect of Quinovic acid obtained from bark of Kadamba or plant of Una de Gato against COVID-19 can be taken and if this shows positive result, a clinical trial can be undertaken for developing efficacious and cheaper drug against the to-be recurrent COVID-19 viral storm.

When the crisis is of global proportion, all modes of knowledge have to be applied to find a solution. Traditional Indian Medicine (TIM) too needs to come out of closet and work on new formulations to tackle the ever erupting new diseases. Any knowledge tradition, once fossilized, loses the relevance during unseen crisis. Silos of superiority must be broken down to adopt and synthesize wisdom from different culture and civilization.

Niraj Kumar

Honorary Editor

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TRENDS IN SOCIAL SECTOR EXPENDITURE IN INDIA (2005-2019)

Mukul Kumar*

ABSTRACT

Unraveling the instrumental aspects behind the trajectory of growth and development, this paper endeavors to conduct a time series analysis of the social sector expenditure in India for the past fifteen years. The paper examines how far has India's commitment to the social sector fared in terms of the expenditure on social services based upon indicator emphasized by UNDP's Report on Human Development. Further, by employing the direct relationship between the public provisioning of social services and an enhancement in individual capabilities, it has been justified why India needs an increase in its social sector expenditure following the economic growth trajectory of successful models of growth.

Keywords: Capabilities, Education, Health, Social Allocation Ratio, Social Sector Expenditure.

INTRODUCTION

Becoming the fifth largest economy in the world, the trajectory of Indian economic growth has improved by leaps and bounds after emerging from the shackles of imperialism. Not only has India witnessed a growth in its economy but this growth has been coupled with a growth in economic inequalities that has concentrated the fruits of development into the hands of a few. On the contrary, there exists within the Indian social fabric a major proportion of the population that still relies on the government for the public provisioning of essential services. Amidst this struggle to sustain significant proportion of population reeling under, the role of the government as a provider of instrumental social and economic services assumes paramount importance for the harmonious development of the masses. Moreover, given the amount of deprivation in the economy it then becomes the social obligation of the government to eradicate the problems of poverty, malnutrition, unemployment and illiteracy by allocating greater amount of resources. Effective social sector expenditure remains a manifestation of government's commitment towards creating a fertile ground for long run economic growth and development.

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Deployment of optimal amounts of funds in the social sectors of priority concern can facilitate an enhancement in the standard of living of the people of the country. Therefore, it assumes utmost importance to analyze how far has India traversed in achieving the goals of social sector in terms of the expenditure that is allocated to the social sector by the government. Trends in the expenditure incurred by the government on the provisioning of social services for the common good reveal how has the commitment of the government changed towards the priority sectors of the social arena over time.

OBJECTIVE

This research paper endeavors to:

- Conduct a time series analysis of the social sector expenditure in India between 2005 to 2019 with a greater emphasis on the priority sectors of health and education;
- Gauge the commitment of the government towards development in social sector through an indicator called Social Allocation Ratio as emphasized by the UNDP;
- Justify the need for adequate expenditure on social sector through the lens of the capability approach as put forth by Amartya Sen.

METHODOLOGY & DATA COLLECTION

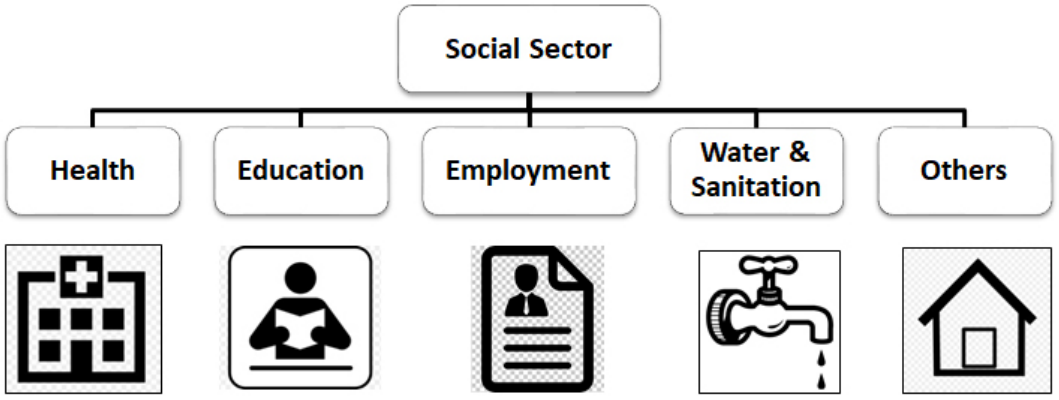
The paper mainly relies on secondary data acquired from the *Economic Survey* and the Union Budget documents of various years along with the annual publications of the RBI. The data used for analyzing the trend ranges from the year 2005 to 2019. For the years 2005 to 2017, Actuals (actual expenditure) have been used while for the year 2018 and 2019 only Revised Estimates and Budget Estimates respectively were available.Simple statistical tools such as percentage, average, graphs have been used to trace and depict the pattern for data interpretation.

MODEL SPECIFICATION

As per the budget documents of the government,social sector expenditure has been defined as a composite of expenditures on Education, Health, Family Welfare, Water Supply and Sanitation, Housing, Urban Development, Labour and Employment, Social Security & Welfare, Nutrition, Welfare of SC, ST and OBC, Natural Calamities, Sports and Youth Services, Arts and Culture, Other Social Services, Secretariat Social Services & North Eastern Areas.

Being a harbinger of development, the social sector primarily comprises of the social and economic activities undertaken for the purpose of benefiting the society at large and can mainly be categorized as non- profit, not-for-profit, philanthropic and mission based activities that prepare favorable pre- requisites enabling the common to subserve.

In this analysis education and health has been considered as the priority sectors of the social arena owing to the far reaching positive externalities that these two major components of the social sector herald for the growth of the economy and society as a whole.



(Source: Self-created)

Figure 1 : Major Components of Social Sector

DATA ANALYSIS

The pattern of expenditure on social services over the past fifteen years can be examined in three ways. First is to look at social sector expenditure as percentage to GDP. The second option is to look at the trends in social sector expenditure as against the total expenditure. Third way is to analyze the trends in the share of the government's expenditure earmarked for social services in absolute terms for a clearer comparison. All three possibilities have been explored in the following possible manner:

1. Social Sector Expenditure as a Proportion of the GDP

With the total budgeted expenditure of the government being 25.99% of the GDP in 2005-06, the expenditure on social services as a proportion of GDP was reported to be 5.49% of the GDP in the fiscal year 2005-06. Ever since that year,it began witnessing an increasing trend, augmenting from 5.57% of GDP in 2006-07 to 6.79% of the GDP in 2010-11 that can mainly be attributed to the allocation of more funds to new government initiatives and an expansion in the coverage of the existing flagship programmes. However, for the next three fiscal years from 2011-12 to 2013 -14, this growth stagnated to 6.6% of the GDP that can be a consequence of the Global Financial Crises that led economies into a lasting recession. Further the allocation decreased to 6.2% of the GDP in the year 2014-15. It is pertinent to note here that this decline in the overall allocations for the social sector in the fiscal year of 2014-15 was witnessed as the government in power slashed the social sector spending to meet their fiscal deficit targets of 3.5% of the GDP. Along with this, the government put forth that more resources were being transferred to states on the basis of the recommendations of the Fourteenth Finance Commission. However this cutback was not adequately prepared for and there were at least short term problems and funds crunch for some important schemes of social sector.Since then the figures for the same give us a glimpse of an increase in the government's commitment towards the social sector as the expenditure as proportion of GDP has only increased reaching 7.7% of GDP as per 2019-20 BE.

Table 1: Trend in Social Sector expenditure as Percentage to GDP

Year	Government's Total expenditure	Expenditure on Social Services	Education	Health	Other sectors
2005-06	25.99	5.49	2.61	1.23	1.65
2006-07	25.83	5.57	2.67	1.21	1.69
2007-08	26.37	5.91	2.59	1.27	2.05
2008-09	28.41	6.76	2.88	1.32	2.56
2009-10	28.59	6.89	3.04	1.36	2.49
2010-11	27.52	6.79	3.13	1.29	2.37
2011-12	27.7	6.6	3.2	1.3	2.2
2012-13	27.1	6.6	3.1	1.3	2.2
2013-14	26.7	6.6	3.1	1.2	2.3
2014-15	26.4	6.2	2.8	1.2	2.1
2015-16	24.7	6.6	2.4	1.3	2.5
2016-17	26.7	6.8	2.8	1.4	2.6
2017-18	26.4	6.7	2.8	1.4	2.4
2018-19 RE	26.8	7.6	3.1	1.5	3.0
2019-20 BE	26.9	7.7	3.1	1.6	3.0

*Data (Actuals) as acquired from *Economic Survey* of various years.
*Figures of 2018-19 are Revised Estimates, while that of 2019-20 are Budget Estimates.

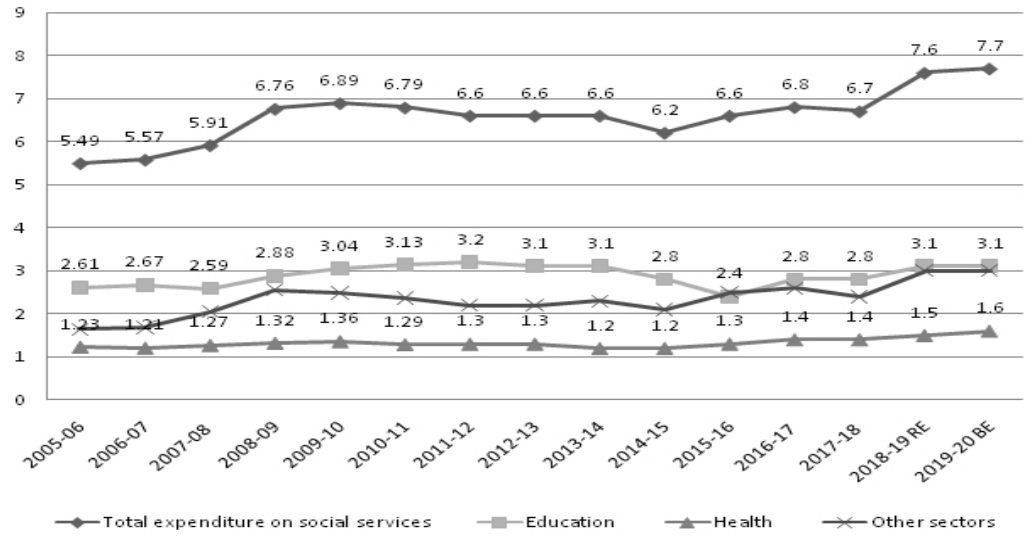
BREAKING IT DOWN INTO EDUCATION & HEALTH

In this analysis education and health has been considered as the priority sectors of the social arena owing to the far reaching positive externalities that these two major components of the social sector herald for the growth of the economy and society as a whole.

As a proportion of the GDP, expenditure on education has increased from 2.6% of the GDP in 2005-06 to 3.1% of the GDP in 2019-20 BE. However the growth has not been a consistent path as there were minor fluctuations in the years in between. Overall we can say that the expenditure on education as proportion of GDP has hovered in the range of 2-3% during the entire period under consideration as shown in the Table above and depicted in the graph below.

Similarly, although the expenditure on health as a proportion of GDP has increased from 1.23% in 2005-06 to 1.6% in 2019-20 BE but at a very sluggish pace. Overall we can say that there has not been any mammoth change in the expenditure on health as it has remained less than 2 per cent of the GDP during the entire period as depicted in the graph below. As suggested by many policy makers, India's healthcare spending is much below its European counterparts that spend around 6% to 11% of their GDP only on Healthcare.

Graph 1: Trends in Expenditure as Percentage of GDP



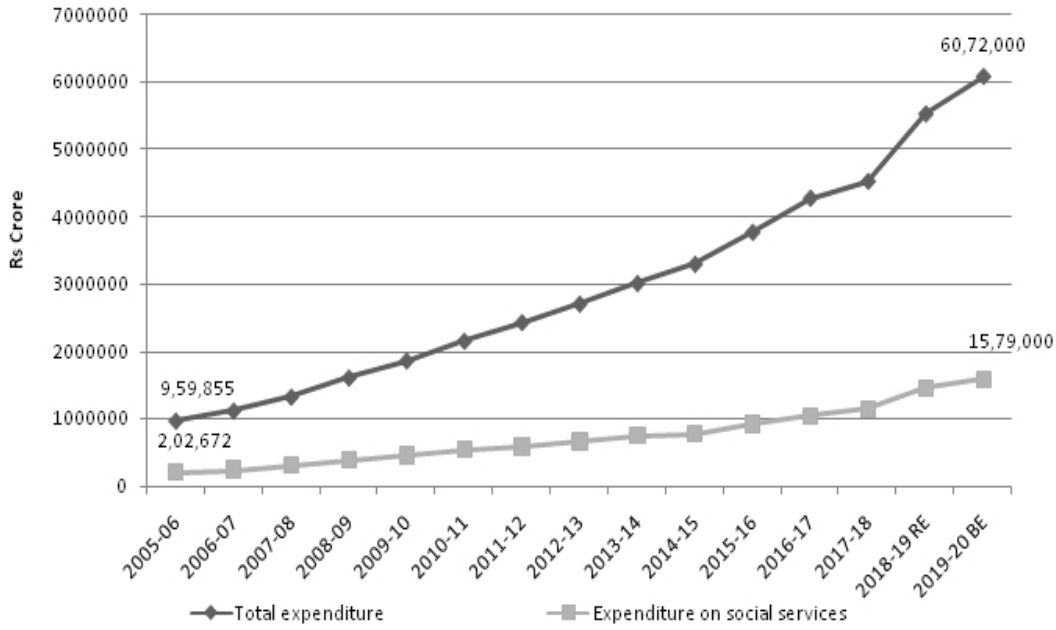
2. Pattern of Social Services Expenditure against Total Expenditure

Over the last fifteen years, the total expenditure by the general government has seen an eight-fold increase in absolute terms as shown in the Table 2. On the contrary, the growth of social sector expenditure against total expenditure has been quite sluggish and it has not been as proportionate as was witnessed in the increase in total expenditure.

Table 2: Trends in Expenditure on Social Services against Total Expenditure

Year	Expenditure on social services (in Rs. crore)	Total expenditure (in Rs. crore)
2005-06	2,02,672	9,59,855
2006-07	2,39,340	11,09,174
2007-08	2,94,584	13,16,246
2008-09	3,80,628	15,99,533
2009-10	4,46,382	18,52,119
2010-11	5,29,398	21,45,145
2011-12	5,80,868	24,21,768
2012-13	6,58,320	26,94,934
2013-14	7,46,391	30,00,299
2014-15	7,67,622	32,85,210
2015-16	9,15,500	37,60,611
2016-17	10,40,620	42,65,969
2017-18	11,40,000	45,16,000
2018-19 RE	14,47,000	55,17,000
2019-20 BE	15,79,000	60,72,000

Graph 2: Trends in Expenditure on Social Services against Total Expenditure



3. Social Allocation Ratio

The UNDP Report of 1991 chalked out an instrumental indicator that can enable us to gauge the commitment of a country's government towards development in social services termed as Social Allocation Ratio that essentially reflects the share of the government's expenditure earmarked for social services.

Social Allocation Ratio = Expenditure on Social Services X 100
Total Expenditure

Total Expenditure

If we attempt to tweak it in per capita terms for facilitating comparison between countries based upon this parameter, we can divide both the Expenditure on Social Services and Total expenditure by the population figure that yields

Social Allocation Ratio = Expenditure on Social Services/Population X100
Total Expenditure/Population

The population component in both numerator and denominator gets cancelled away and we again arrive at the same formula as emphasized by the UNDP Report proving that it is sustainable as a measure to facilitate comparison between different countries.

The Report further sheds light on the aspect that countries having high level of human development have an optimal level of 40% as their Social Allocation Ratio.

Table 3: Trends in India's Social Allocation Ratio

Year	Social Allocation Ratio
2005-06	21.11%
2006-07	21.57%
2007-08	22.28%
2008-09	23.79%
2009-10	24.10%
2010-11	24.68%
2011-12	24.00%
2012-13	24.43%
2013-14	24.88%
2014-15	23.36%
2015-16	23.39%
2016-17	24.24%
2017-18	24.89%
2018-19 RE	26.22%
2019-20 BE	26.00%

Focusing on the Indian growth story, India's Social Allocation Ratio has shown an increasing trend from 21.11% in 2005-06 to 26% in 2019-20 BE. The figure has increased by around 5% during the entire period under consideration. However, the Social Allocation Ratio has never crossed the benchmark of 26%. This further gives us a sufficient understanding of the fact that why India still continues to remain a consistent low rank holder as per the Human Development Index values constructed by the UNDP that is apparently well below its peer countries such as Sri Lanka and other South- East Asian countries

MAJOR FINDINGS OF THE ANALYSIS & KEY SUGGESTIONS

Considering the changes in the allocation of funds to the social services by the Indian government, it was observed that during the entire period under consideration, i.e., between 2005 and 2019, the social sector expenditure has risen by 6.8% (as per the absolute figures). This increase can mainly be attributed to the allocation of funds to new initiatives by the government and an expansion in the coverage of government's flagship social welfare schemes. However, the growth has been sluggish.

A trend has been observed in the budget documents that every year the initial allocations in the budget (Budget Estimates) are greater while the actual expenditure (Actuals) that is reported after a year is much lower than the initially allocated amounts. This presents before us a dismal picture arising out of the process of allocation of budget every year. Moreover, it has been observed that the decrease has been greater for the social sector schemes.

The path to an augmentation in the social sector expenditure is but a path laden with pitfalls owing to the fragility of expenditure on social services in India. There is a greater commitment of the government for the containment of its fiscal deficit to keep it within the range of 3.5% of the GDP as stipulated by the Fiscal Responsibility Budget Management Act of 2014. However, there is no constitutional regulatory framework that serves as a guiding light for the government expenditure on social services and keep it within certain prescribed limits. A major ramification of this loophole is that as and when the fiscal deficit of the government looms large, the government does a cut back on the social sector expenditure to meet their fiscal deficit targets leading to a brazen crowding out of essential expenditure on public provisioning of social services. There is a need to fill this void with an appropriate mechanism to set a minimum floor on social sector expenditure by the government. The remedy of this cyclic ailment is stringent policy imperatives that strengthens fiscal consolidation and aims to curtail the fiscal deficit and having a surplus budget that can equip the government with the ability to allocate adequate amount of funds to the social sector. A sufficiency in terms of availability of funds will leave no room for the government to resort to a cutback on social sector expenditure. This reiterates the need for fiscal consolidation as this would provide more headroom to the government for carrying out social sector expenditures during phases of slowdown in economic growth.

A close evaluation of the composition of social sector expenditure reveals that a major chunk of this expenditure falls under the head of Revenue Expenditure that is regular and recurring in nature such as the salaries of employees and regular disbursement of transfers that leaves the asset liability situation of the government unchanged. However, the Capital Expenditure that essentially leads to creation of assets or reduction of liabilities constitutes a very insignificant portion of the total social sector expenditure. Thus the government should strive for greater creation of assets for the common good.

As calculation of Human Development Index does not take into account the amount of inputs that are invested for growth in the social sector rather it focuses on evident outcomes such as life expectancy at birth, mean years of schooling and per capita income. Thus, mere allocation of funds will not improve India's HDI ranking rather it has to be coupled with improvement in the indicators of social sector that can only be achieved through greater commitment of the government. How the money allocated is being spent is also a very crucial aspect which needs to be considered. We cannot solely rely on increasing amount of social sector allocations. Rather, after the allocation of more funds, the focus should be on proper utilization of these funds for achieving the desired targets and their channelization through schemes and policies that are well implemented and allow the proposed benefits to reach the targeted beneficiaries. Therefore, greater allocation of funds towards the social sector is only a necessary condition for achieving equitable economic growth and should not be regarded as a sufficient condition for economic prosperity.

NECESSITY OF HIGHER SOCIAL SECTOR EXPENDITURE: THE CASE OF INDIA

Viewing social sector expenditure through the lens of the capability approach of Amartya Sen, endows us with the opportunity to evidently establish a direct relationship between provisioning of imperative social services by the government and an enhancement in the capabilities to achieve higher economic growth.

As per the capability approach, an individual enjoys the advantage of leading the kind of life she values with substantive freedom that her capabilities bestow upon her. And income remains an instrumental means to enhance capabilities. While lowness of income can be the principal reason leading to deprivation of basic capabilities by creating a myriad of ramifications and exacerbating the existing forms of inefficiencies. On the contrary, endowment of adequate levels of income can serve as an essential channel for capability improvement. Enhanced capabilities and greater earning potential that are achieved due to greater access to education, healthcare and social provisioning of pivotal services can substantially improve the standard of living of the masses.

The biggest testimony to substantiate this claim remains the growth trajectory of the Indian state of Kerala. A state that was once considered to be an outlier due to its socio-cultural practices that are distinct from the rest of the country now happens to lead the country in the social indicators of education and health. This transition can only be attributed to the reinforced focus of the government on the priority sectors of health and education. In Kerala, expansion of public provisioning of basic education, health and other social services not only led to the reduction of poverty but has also facilitated the rise of Kerala in terms of Human Development Index and the standard of living of the rank & file making its growth story an ideal model that can be replicated by other states as well for facilitating the trajectory of development. Kerala's transition stands as a testimony to the fact that expenditure on social services is the best way for achieving economic growth.

CONCLUSION

In the case of India, the Government's expenditure on social sector assumes importance on three accounts. The first being magnitude of deprivation in the country being too large to be left to the market forces alone to tackle. Secondly, the proportion of poor households utilizing Government services is higher as compared to the richer households and thirdly, to ensure clearly articulated outcomes in social sectors such as the Sustainable Development Goals (SDGs).

A growth in the income level that uplifts the standard of living remains a stepping stone for higher economic growth and investments in the social sector of education, health, employment, social security, etc. This will not only enhance the capabilities of the masses but will also bring them out of the shackles of poverty, deprivation and the vicious cycles of drudgery, facilitating their betterment through enhanced capabilities and earning potential. A well-financed social sector should remain the utmost priority of the government to prepare reinforced socio-economic foundations of a population that is enabled to reap the benefits of good health, literacy, employment, social security and better cognitive skills & an enhanced potential to pave their way towards development.

Policy imperatives of eminent economists and research scholars can be a guiding light in this pursuit. While Amartya Sen believed that the Centre needed to invest more in social infrastructure to boost productivity and consequently raise growth, on the contrary Jagdish N. Bhagwati believed that only a focus on growth could yield the resources needed for investing in the social sector. This masterpiece of economic growth and development can be painted

on the canvas of time through greater commitment of the government towards the priority concerns of social sector that is reflected through the level of expenditure on them.

India being on the brink of a demographic revolution and a larger amount of young people in the productive age group, education and health assume great significance on account of their real contribution to production by ensuring rapid and inclusive growth. Therefore, in order to reap the benefits of India's growing demographic dividend, there is a need for higher public spending in the social sector, especially key areas of education, health and sanitation. The government needs to move beyond rhetoric to leverage the favorable consequences of this demographic transition

A higher spending in the social sector, particularly on education and health, is absolutely essential for inclusive and sustained growth. Improving the quality of the two key development indicators will create the requisite pressure to ensure that the high economic growth is both inclusive and sustainable. A better educated and healthy population will mean improved productivity.

Government investment in social sectors has always been an important factor in tackling social issues and facilitating the alleviation of poverty. Hence, for the greatest good, budgetary expenditure for such investment needs to be efficiently allocated and utilized.

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ROLE OF INDIA'S TECHNOLOGICAL INNOVATIONS TO MITIGATE COVID-19 PANDEMIC

Dr. Manish Mohan Gore*

ABSTRACT

Science unfolds the secrets of nature while technology makes the human life easy. Innovation is the third dimension after science and technology. Through innovation, new ideas are successfully exploited. In fact innovation is a new and vibrant idea which supports human lives. Technological innovations have become the boon for the humanity. Several such innovations are serving the humans to treat ailments, enhancing entrepreneurship and development of nation. During COVID-19 pandemic, technological innovations have played vital role to mitigate its impact. Such innovations have saved billions of human lives. In this study, the prominent technological innovations of India have been discussed which are worthwhile to combat COVID-19. These innovative technologies, drone, robot, Apps and multimedia digital platforms are developed by a number of scientific laboratories academic institutions of India which belong to both public and private sectors.

Keywords: App, COVID-19, digital platform, drone, entrepreneurship, innovation, multimedia, pandemic, technology.

INTRODUCTION

Homo sapiens is the most intelligent life on earth. This species scattered throughout the world and established itself. Apart from human brain, inclusion of science and technology has shaped the human progress. In fact the logic and mental exercise of humans are at the roots of science and technology. Innovation is third dimension in it. Uncovering the secrets behind natural phenomenon is known as Science (derived from the Greek word *scientia* means 'to know'). Technology concept is the brain child of humans. It provides the tools, instrumentation techniques and methods to perform scientific theories and apply in real-world adaptation. The technological attainment remarkably improves the quality of life and aids social advancement in almost everything (G. Giacomelli and R. Giacomelli, 2004). The inventions in the field of transportation have made human life more comfortable. The modern technologies have drastically changed the sectors of health & medicine research, space exploration, banking, commerce and communication. Biotechnology, Augmented and virtual reality, Internet of things (IoT), Quantum computing, machine learning, artificial intelligence and robotics are emerging as the newest technologies from the beginning of 21st century (UNESCO, 2012).

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Innovations are reflected in the form of creative thoughts and new imaginations in the form of new method, device or product. This has the strength to reshape the society. If wind flow is science, fans are technology, and then the wind turbine is the example of innovation. Technological innovations are instrumental in sustainable development. Through science, technology and innovation, the world steadily reaches to a more modernized future (Sasvari P, 2012).

Technological innovation helps human being in many ways. It combats social problems like poverty and unemployment by introducing entrepreneurship and small-scale industry (*Kutir udyog*) in villages (Sang M Lee and Silvana T, 2018). It also mitigates health problems and medical emergency such as COVID-19 pandemic. Innovative technologies are used in the development of drugs and vaccines. The development of life-saving products like drugs and vaccines is a time taking process. It has many stages and trials to reach up to a flawless end product to be used on a large population. We reach to the drug and vaccine stage at the end. Prior to that final stage, the mitigation, containment, diagnosis and testing are some conclusive factors for the disease control. During any infectious disease or epidemic, these factors are very much crucial and technological innovations address those to contain the infection and mitigate the effect of epidemic (Janmejaya S, 2014). COVID-19 presents a good example of this. Innovative technologies developed by several nations of the world including India during this pandemic have played pivotal role to reduce the mortality as well as mitigate the pandemic impact (Brohi SN *et al.,* 2020). A number of Indian science and technology laboratories have developed many tools, technologies, App etc. during COVID-19.

TECHNOLOGICAL INNOVATIONS EASE THE HUMAN LIFE

Earlier in the twentieth century, electricity and means of transportation were big inventions that have changed the human life. Later internet and ICT revolutionized the world. Internet has become the essential thing just as oxygen for our life. Today, technology is embedded in everything we do. It impacts the way we live, work and experience the world. The journey of exploration, invention and innovation allows them to integrate its applications into human life. Technological innovations have altered the world entirely. It becomes the foundation of tools and techniques that support a more efficient engineering purpose and design(Sasvari P, 2012). In addition to research instrumentation and analytical processes, such innovations are used in industrial practices, skill development and entrepreneurship. Technology has transformed the education and knowledge-based information system and it has the huge social impacts(Banking Technology Vision, 2018).

The advancement of technology brings unprecedented improvement in the field of healthcare and medicine sector. A number of incurable diseases like tuberculosis are now treatable. The medical procedures and diagnosis have become more reliable and safe because of the modern precise and accurate medical tools. Advancement in technological innovation has given to human a much better existence (Fett M, 2000). We are living in a world of technology and technological innovation is reshaping our society manifold. Technological innovation affects all walks of human life from agriculture to transportation and communication. Innovation improves quality of life even if any person is facing income

lag. Global improvements in quality of life have been enhanced by the spread of technology and innovative ideas. Very cost effective health technologies that can dramatically reduce mortality are accessible across the world. The proportion of the world's infants vaccinated against pertussis, diphtheria, tetanus (DPT) climbed from one fifth to nearly four fifths between 1970 and 2006. Simultaneously the ideas that save lives such as to wash one's hands, to not defecate in the open are increasingly accepted. The fast pace developing countries like India has witnessed the improved quality of life which results from technological innovations (Charles Kenny, 2009).

Dire necessity is the precursor of any innovation. Famous scientist Stephen Hawking had once said that probably in time-period of 100 year, the earth will not be inhabitable for humans. Population explosion, resource shortage and climate adversities will bring this situation. As per the speculation of Hawking, in that circumstance, the shifting of earth's population to other conducive nearby planets could happen. Colonization in other planets will be the big leap of technological innovation and in coming future, this can be a reality. Many scientists of the world consider this as a science fact rather than science fiction.

Robots are a best example of innovation in technology. In coming future, robots will do many jobs at workplace as well as in homes efficiently, more quickly and with fewer mistakes too. Use of the robots in space research, healthcare and industry is very promising. Electric vehicles have become reality and in recent future, one will no longer need to commute oneself. Take a nap, let the car run automatically. Self-driving cars is going to become a reality. Road congestion with heavy traffic has become a big challenge. Don't worry flying cars is the next possibility (Roberts J and Milford M, 2017).

IMPORTANCE OF TECHNOLOGY DURING COVID-19

COVID-19 has posed a huge challenge before the world from February 2020. Most of the countries are in the grip of novel corona virus. First case of this viral infection was reported in Wuhan, China in December 2019. To combat the COVID-19 outbreak, the development and implementation of technology solutions aimed at are rapidly taking shape around the world. Governments, industries, research & academic institutions, incubators, start-ups are all doing their part to deploy new innovative technological solutions (Kritikos M, 2020). In order to contain the novel corona virus, governments are developing and modifying policies to promote the rapid development of technologies. The companies are supporting fund for the new innovative technologies in the fight against the COVID-19 pandemic under the Corporate Social Responsibility (CSR).

In India, the Social Impact Team at Invest India is augmenting the efforts of the MCA by collating a repository of CSR eligible innovations that can help in testing, curing and prevention of COVID-19 (CSR Funding for Technology Incubators blog).

The United States has allowed the Food and Drug Administration (FDA) to expedite the use of new medical devices during public health emergencies. During corona crisis, this effort is now empowering companies to deploy innovative medical devices to market rapidly. Abbott Laboratories has developed an innovative technology namely portable 5-minute COVID-19 test kit with the size of a toaster. The test kit is now being used across the U.S. This innovation

will help in testing the untested COVID-19 patients. These are a few snapshots to reveal the significance of technology in the pandemic.

Any epidemic can be won by three major weapons. One is drug or vaccine, second is technological interventions and third one is scientific temperament among the common people. Technology plays a crucial role to mitigate the epidemic. No country can have sufficient number of ventilators, PPE, N95 masks, ICU and hospital beds to handle any epidemic situation. Therefore vaccine, technological innovations and scientific outlook are key factors to overcome epidemic crisis. When the number of cases increases during the spread of epidemic, shortage of the ventilators, ICUs etc. start occurring. In this situation, technological innovation in the essential medical equipment become instrumental and it plays conclusive role in outbreak mitigation. Hence the importance of technological innovation cannot be ignored at the time of epidemic.

INDIA'S TECHNOLOGICAL INNOVATIONS THAT MITIGATE THE IMPACT OF COVID-19

Indian S&T laboratories such as the Indian Council of Medical research (ICMR), Council for Scientific and Industrial research (CSIR), Department of Science and Technology (DST), Department of Biotechnology (DBT), Defense Research and Development Organization (DRDO), other scientific and academic institutions as well as private sector enterprises of the country are bringing many technological innovations in response to COVID-19. Apart from this, entrepreneurs and innovators have quickly devised new apps, robots and ventilators to help overcome the pandemic across the country. A few innovations are emerging from start-ups that have been incubated by universities and IITs.

Digital Surveillance to monitor the COVID-19 Spread

Two of the CSIR labs namely the Centre for Cellular and Molecular Biology (CCMB) and the Institute of Genetics and Integrated Biology (IGIB), along with a few other institutions, are working for the digital and molecular surveillance of the spread of novel corona virus to understand the biology, epidemiology and disease impact. With digital and molecular surveillance of novel corona virus, scientists are hoping to get some clue for many of the unknowns today. The centre is established at IGIB where all the labs, research centres and hospitals will share their data through cloud sharing (CSIR News, April 2020).

App, Drone, Robot and ventilator

During COVID-19 pandemic, different mobile applications have proved extremely useful to inspire people about the hand hygiene, social distancing and following lockdown rules. In early April this year, the Indian government launched a Mobile App *Aarogya Setu* which uses GPS and Bluetooth to inform people when they are at risk of exposure to COVID-19 (Sankaranarayanan KB, 2020). This App gives input in 12 major Indian languages. Within three days of its launch, more than 5 lac people downloaded this useful App.

Dr.Tavpritesh Sethi at IIIT (Indraprastha Institute of Information Technology) Delhi and his team have developed an android-based mobile App *Wash Karo* that functions as a complete Infodemic Management Suite. This App was presented at WHO, Geneva on

8 April 2020, via video conferencing. This App aims to help aware the public about the COVID-19 pandemic. The updated content of this App is delivered in the form of byte-sized audios for those who may not be able to read (COVID-19 Newsletter, *Vigyan Prasar,* 30 April 2020).

Similarly many state governments and other government organisations have developed mobile Apps to combat COVID-19. Their objectives include patient tracking to healthcare services. A few names of these Apps are COPE Odisha, Corona Mukt Himachal, COVA Punjab, Covid Care Kerala, Haryana Sahayak, mCOVID-19, UP Self-Quarantine App, Test Yourself Goa, Kavach, Driver Seva (COVID-19 Apps from India, e-Book, CSIR-NISCAIR, 2020).

One of the DRDO laboratories, Centre for Artificial Intelligence and Robotics (CAIR), Bengaluru has created a technology based solution to track COVID patients who are under quarantine. A team of 20 scientists have developed the SAMPARC App in three weeks. SAMPARC stands for Smart Automated Management of Patients and Risks for COVID-19. The App has already been offered to various state governments to enable AI-driven measures to reduce the outbreak. SAMPARC is the software that includes an App that would be installed on the smartphones of the patients. This technological innovation is expected to drastically reduce the overhead of tracking every COVID patient under home isolation and in this way; load on the state machinery will be reduced. With SAMPARC App, the officials can easily track the violators and can also perform random checks (COVID Newsletter, *Vigyan Prasar*, 23 April 2020).

The Central Road Research Institute (CRRI), a CSIR laboratory has developed an app called '*KisanSabha*' to resolve the problems related to the agricultural supply chain during the COVID-19 pandemic and lockdown situation in India. This useful mobile App acts as a one-stop technological solution for farmers, transporters and other entities engaged in the agriculture sector. For its implementation, the Indian Council of Agriculture Research has used the vast network of Krishi Vigyan Kendra (KVK) in the country (Mishra, Umashankar; 2020). In April 2020, the Union Agriculture Ministry of India had introduced a mobile App '*KisanRath*' for the farmers in India during nation-wide lockdown. The App provides assistance to Indian farmers and traders, transport produced goods during the ongoing corona virus pandemic. The *KisanRath* mobile App helps facilitate transportation by onboarding 5 lakh trucks and 20,000 tractors on the online service (Ansari, Danish;2020).

To sanitize big compounds of school, hospital, airport or government offices through a manual spraying process approach is very difficult. To resolve this difficulty, the Office of the Principal Scientific Adviser (PSA), Government of India and *Invest India* have initiated Corona Killer 'Drone CK100'. This drone has been developed by the Garuda Aerospace. It is an Automated Disinfecting Technology that aids in sanitization of public places, hospitals and tall buildings. Drone operations are faster, longer and safer than manual spraying workers who can become potential carriers of COVID-19. Drones reach heights up to 450 feet and spray disinfectants on buildings which are impossible manually. This effective technological solution prevents the spread of COVID-19 as well as communicable diseases arising due to unhygienic conditions. Using drones, authorities could spray disinfectant over a large,

crowded and vulnerable urban area. This technology protects city dwellers from COVID-19, while reducing human contact to keep frontline workers safe (COVID-19 Newsletter,*Vigyan Prasar,* 23 April 2020).

A number of doctors and healthcare workers are getting corona infection. They have great risk of infection while taking care of COVID patients. Durgapur (West Bengal)- based CSIR lab, Central Mechanical Engineering Research Institute (CMERI) has developed an innovative robotic device HCARD (Hospital Care Assistive Robotic Device) which is helpful to the frontline warriors in maintaining physical distance from corona virus infected patients. The device is equipped with various state-of-the-art technologies. It works both in automatic as well as manual modes of navigation. This robot can be controlled and monitored by a nursing booth with a control station having innovative features such as navigation, drawer activation for providing medicines and food to patients and sample collection. Through this device, healthcare workers can also do audio-visual communication with the patients. (COVID-19 Newsletter, *Vigyan Prasar,*30 April 2020*)*.

During COVID pandemic, a team of scientists at CAIR, DRDO has quickly customized a cost effective robot '*Sewak*' within a week. It can be a safe alternative for the healthcare staff taking care of the COVID-19 patients in the quarantine centres and hospitals. *Sewak* can be tele-operated by the hospital staff from a remote location to navigate the quarantine zone and distribute food, water, medicine etc. to the affected persons. The robot gets power from rechargeable batteries and can work continuously for 5 hours on full charge. Video camera fitted in the front helps navigating to the patient's bed. Audio facility provided in the robot facilitates two-way communication between the patient and the healthcare staff (COVID-19 Newsletter, *Vigyan Prasar*, 30 April 2020).

Asimov Robotics, a start-up based in Kerala, has also deployed robots during COVID pandemic. These robots are used at the entrances to office buildings and other public places to dispense hand sanitizer and deliver public health messages about the virus. Robots deployed in isolation wards of the hospitals are assisting to carry medicines and food items (Rekhi D, 2020).In India, during the COVID pandemic in response to the shortage of ventilators for critical care, start-ups like Aerobiosys (incubated at IIT Hyderabad), Nocca Robotics (incubated at IIT Kanpur) and AgVa Healthcare have developed the cost effective, easy-to-use and portable ventilators that can be deployed even in rural areas of the country (*Industrial Automation,* 2020).

Testing Kit, PPE and Textile with anti-Microbial Material

CSIR-Institute of Genomics and Integrative Biology (IGIB), New Delhi has developed a portable, rapid and cost-effective paper strip based test kit called FELUDA. CSIR and Tata Sons have now signed a MoU for licensing the technology for scale-up and deployment in usable kits (COVID-19 Bulletin, CSIR-NISCAIR, 12 May 2020).

The RNA extraction kit called *Chitra Magna*, has been developed by Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), an institution of the Department of Science and Technology, Government of India. This is an innovative technology for isolating RNA from swabs for COVID-19 tests (COVID-19 Newsletter, *Vigyan Prasar* ,30

April 2020).

CSIR-National Aerospace Laboratories (NAL), Bengaluru has developed a coverall protective suit for protection of healthcare workers. The polypropylene spun laminated multi-layered non-woven fabric suit has been developed in collaboration with MAF Clothing and has undergone stringent testing. MAF Clothing intends to manufacture 30,000 units per day of the cost-effective protective cover all suit. (COVID-19 Bulletin, CSIR-NISCAIR, 2 May 2020). IIT Madras incubated start-up '*Muse Wearables*' has created coated-textile with anti-microbial material to be used in the manufacturing of N95 masks, surgical masks, PPE, food packaging bags, etc. The coatings are expected to be effective up to 60 wash cycles, thereby making the textiles re-usable.

Tele-medical Consultation Portal

Visiting a health centre or hospital for any kind of ailments has become a new challenge due to the high risk of possible COVID-19 infection. Doctors are also naturally cautious and sensitive about examination of patients. However, such situations provide opportunity for technology to usher in new solutions. At Indian Institute of Technology Jodhpur (IITJ), Kunal Tawatia, an undergraduate student of the CSE Department, under the mentorship of Dr Sumit Kalra has developed a tele-consultation platform. Utilising this platform, one can consult doctors for ailments (COVID-19 Newsletter, *Vigyan Prasar*, 30 April 2020).

Foot-operated Washing Station

Handles, knobs, doors, electric switches, water tap etc. are the common use surfaces in our daily life. During the COVID pandemic, these surfaces are major sources of disease spread in the community. The foot-operated hand washing stations are technological innovation where direct surface touching is not required. It is recommended to install at all public areas to enable residents to frequently wash their hands.

Foot-operated Washing Station has been implemented at the Indian Astronomical Observatory (IAO), Hanle, Ladakh (COVID-19 Bulletin, CSIR-NISCAIR, 2 May 2020). IAO has one of the world's highest located sites for the optical, infra-red and gamma-ray telescopes. Bengaluru based autonomous body of DST, the Indian Institute of Astrophysics (IIA) operates this observatory. These foot-operated hand washing stations will control the spread of the disease while reducing amount of water used. Again there is another innovation for minimal use of soap and for this chlorine has been added to the water.

***Suraksha Kawach* – An IoT device for Corona Patient Tracking**

Defence Research and Development Organization (DRDO) has developed an IoT device '*Suraksha Kawach'* for corona patient -tracking and their surveillance. It is an ankle or arm band based customised IoT solution. *Suraksha Kawach* is a tamper-proof solution for tracking the COVID-19 patients. It is a GSM and GPS- enabled rugged system for real-time tracking. It is an integrated solution with software for central monitoring and management. It is enabled with geo-fencing, tampers detection, battery status monitoring, mechanism for alerts to urban local bodies, police and distributed alert mechanism. The device can also be integrated with *Arogya Setu* or any other mobile App through server

feeds or by introducing a Bluetooth low energy chip in the current design (COVID-19 Newsletter, *Vigyan Prasar,* 30 April 2020). The unit has battery capacity to withstand quarantine period of 21 days or more, so the device need not be removed for charging purpose. This device is efficient and cost effective.

ATULYA — Microwave Steriliser

Defence Institute of Advanced Technology (DIAT), Pune, has developed a cost-effective microwave steriliser named 'ATULYA' to disintegrate novel corona virus by using differential heating in the range of 560 to 600˚C temperatures. The developed products can operate in portable or fixed installations and can be used for non-metallic objects only. The sterilisation time is from 30 seconds to one minute depending upon the size and shape of the objects (PIB 2020).

Device to Track Coughing Person

Two undergraduate students of the Jadavpur University have developed a smart non-contact device with embedded image and sound sensors. It can track coughing persons and also analyse them for COVID-19. The person can be tracked even when he or she is far away from the device. It is also capable of identifying multiple coughing persons at the same time. The device can be used in quarantine centres, offices or schools for monitoring the people and children present there (*The Economic Times,* 2020).

***COVID KATHA* — A Multimedia Guide for Scientific Awareness**

The National Council for Science & Technology Communication (NCSTC), Department of Science and Technology (DST), Government of India has launched *COVID KATHA*, a multimedia guide on A to Z scientific information on COVID-19 (NCSTC, DST, 2020). To make people scientifically aware about the COVID-19 pandemic in an interactive manner, NCSTC (DST) in association with Dr. Anamika Ray Memorial Trust (an educational and research organisation), has come up with this innovative multimedia guide on COVID-19 which makes people aware about the health and social crisis.

Covid-19 Test Bus

In an initiative to combat the surging coronavirus cases in Mumbai which is one of the worst-hit areas, an IIT Alumni Council has launched India's first 'Covid-19 Test Bus in Mumbai'. This innovative Test Bus is based on the indigenous Kodoy Technology Stack and executed by partner organizations led by IIT Alumni (Sindwani P, 2020). To accelerate the rate of testing, the bus will roam around the city collecting test samples for rapid testing.

CONCLUSION

Technological innovation has great potential to serve the human life. But in a crisis like COVID-19 pandemic, its importance is accentuated several times. In pandemic, any technology is developed with the sole purpose of maximizing the safety of human life. During the crucial situation of COVID-pandemic, all the affected nations of the world including India are developing several innovative technologies to save their citizens. Indian scientists and technologists have worked round the clock and developed a spectrum of innovative technologies to combat COVID-19. In this study, major technological innovations out of those have been discussed.

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COVID-19 PANDEMIC: TRACING THE BEGINNING OF CORONA VIRUS OUTBREAK

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ABSTRACT

The paper encapsulates the initial phase of the outbreak of the Covid-19 pandemic in Wuhan, China. The result from genetic sequences from early samples has also been described. The political noise around the outbreak has been summed up for better understanding about the spread of the pandemic.

Keywords: Covid-19, Gene Sequence, Wuhan, Wuhan Institute of Virology, WHO.

INTRODUCTION

The worldwide outbreak of corona virus has brought major global economies on their knees. The outbreak has already infected more than 7.5 million people and 421,456 people lost their lives as on June 12 across the globe according to the data published by Center for Systems Science and Engineering (CSSE) at John Hopkins University. According to China's National Health Commission (NHC), the country has reported 82, 249 confirmed cases and 3341 deaths out of which 77, 738 recovered and being discharged from hospitals. The outbreak is considered to have originated in the city of Wuhan located in Central China's Hubei province. According to initial investigation Chinese authorities has pointed out the link of corona virus to the "Huanan seafood market" infamous for selling trafficked wild and exotic animals in unhygienic conditions. Initially United States and some other countries demanded independent investigation to trace down origin of the Covid-19 which WHO initially refused but later accepted to do so amidst pressure. The intention of this article is to trace down the origin of corona virus outbreak citing some exclusive reports, published scientific papers within China and worldwide. During the outbreak series of abnormal events happened in China which drew attention of many experts such as Joshua Philipp who has been working on Communist Party of China's espionage and warfare from one decade. He even raised question on official figures given by Chinese authorities after citing censored videos, reports and pictures and warned that situation in China is even worse than what the regime is trying to show.

The first thing that received public attention about the epidemic was an internal notice of "Wuhan Health Commission" on December 30, 2019 which mentioned about unknown pneumonia cases at "Huanan Seafood Market". Next day, the Health Commission had issued

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a public notice for the first time saying that some medical institutions found link between the pneumonia cases and seafood market with no human to human transmission. On January 1, 2020 the seafood market was closed followed by thorough clean-up and it was seized for investigation. On January 26, 2020, Center for Disease Control (CDC) lab of Wuhan Institute of Virology said that 33 out of 585 samples from seafood market were found to contain novel corona virus suggesting that the virus could have originated from wild animals sold at market. At this point "Huanan Seafood Market" was being suspected as source of epidemic. However few days later a paper published in *Lancet* journal, a popular medical journal entitled "*Clinical features of patients infected with 2019 novel corona virus in Wuhan, China*" in which the authors claimed that novel corona virus does not have any links to seafood market. The interesting fact is that the first author of this paper is Prof. Chaolin Huang, the Deputy Director of Jin-Yin-Tan hospital of Wuhan. The hospital is one of the first medical institutions which were designated by authorities to treat novel corona virus patients. Furthermore, the paper made another shocking claim such as symptoms onset of first patient had no relation to seafood market, no links between first and later cases and lastly no one sells bat at "Huanan Seafood Market". According to "*New England Journal*", 45 patients who were reported before January 1, had no history of exposure to the seafood market. According to Daniel Lucy, an epidemiologist at University of Georgetown, the first human infection must have occurred in November 2019 because there is an incubation period between infection and symptoms. If so, the virus possibly spread silently between people-to-people in Wuhan and perhaps elsewhere before the cluster of cases reported in infamous seafood market was discovered in late December 2019. The experts from National Health Commission after studying cases from Jin-Yin-Tan hospital, Wuhan has set up criteria to confirm the cases i.e. 1) A history of contact at seafood market; 2) a fever; 3) whole genome sequence after knowing the hospital has stipulated the history of contact. On January 18, 2020 the second group of experts from Health Commission made a revision and removed the first step of criteria i.e. a history of contact at seafood market. They even questioned why did first panel make it compulsory to include history of contact to confirm the case knowing at least every third case in unrelated to seafood market. Many global experts saw this move as Chinese authorities' deliberate attempt to make seafood market as source of outbreak and intentional cover up of important source of information by imposing false narrative.

AN INSCRUTABLE GENE SEQUENCE

On January 10, China officially disclosed genome sequence of corona virus. After that many virologists from world began to analyze it. As early as on January **7,** an academic group from National Institute of Communical Disease Control and Preventing along with School of Public Health of Fudan University submitted a joint paper to "*Nature"* journal. The title of paper was "*A new corona virus associated with human respiratory diseases in China*" which was published on February 3 and they made a shocking claim that the corona virus is closely related to the two viruses (CovZC 45 and CovZXC 21) sampled from bats in Zhoushan by People's Liberation Army. The corona virus has 89.1 % nucleotide similarity with CovZC 45 virus and exhibit 100 % amino acid similarity in the nsp 7 and 'E' protein. Soon after this, the other scientist used "BLAST", a program developed by National Institute of Health

and National Center for Biotechnology Information of USA and compared the gene sequence and the results were matched with above paper. The earliest discovery of bat-derived virus was conducted by experts from Institute of Military Medicine from Nanjing command. The paper was published in 2018 entitled 'Genomic characterization and infectivity of novel SARS like corona virus in Chinese bats collected from Zhoushan city'. In short, scientist found Wuhan corona virus i.e. the current pandemic is highly similar to bat SARS-like corona virus previously discovered by Nanjing Military Research Institute showing 100% amino acid nsp7 and 'E' protein similarity. Scientifically there is no way the virus can show 100 % similarity when it jumps from species to species bolstering the fact that the virus could have generated with reverse engineering process.

On January 23, a researcher from Institute Pasteur of Shanghai of Chinese Academy of Science published paper in *Science China* (Life Sciences) journal. In this paper, they have mentioned that the sequence of S- protein of Wuhan corona virus has high homology with SARS virus. The 'S-protein' also known as spike glycoprotein are the most important tool of corona virus to invade human cell. The S-protein can easily unlock the receptor on human cell and invade the cell to propagate it and destroy it. The high similarity between S-protein of SARS-1 and SARS-2 which is *lock and key* of virus to enter human body. So now with S-Protein, the access to human tissues is allowed though spike protein of natural strain don't infect human at all. The research on this was going on in Wuhan since 2007 and it was published in international journal which gives strong evidence the virus couldn't go though 'Huanan Seafood Market'. According to the *South China Morning Post*, a media outlet in Hong Kong reported that the Chinese laboratory which first shared corona virus genome with world was ordered to be closed by Chinese authorities for rectification hindering its Covid-19 research. Prof. Zhang Yongzhen who disclosed the gene sequence of corona virus was working in the same laboratory. According to *Caixin* website, on January 5 Prof. Zhang Yongzhen's team isolated and completed the genome sequence of previously unknown virus which is now knows as corona virus. On the same day, the Shanghai Public Health Clinical Center reported this discovery to National Health Commission and recommended preventive measures. But no response was received from authorities. On January 11, Prof. Zhang Yongzhen and his team decided to publicize the genome sequence and became the first to do so. On January 3, China's National Health Commission distributed Notification Letter number 3 in which they have directed that "Existing virus samples must be destroyed, information about the samples, related paper and data are all prohibited from release". After that once active Chinese science community fell into utter silence. All these indicates that Chinese government tried to hide, censor information about the novel corona virus which puts a question mark over the response of regime to tackle the pandemic.

THE SHOCKING DISCOVERIES OF DR. SHI ZHENGLI

Dr. Shi Zhengli is a well-known virologist who is a researcher at Wuhan Institute of Virology in Chinese Academy of Sciences. She was the first to locate the key as to how corona virus can overcome cross-species barriers in order to directly infect human bodies. She was the first to discover that the SARS virus was the result of restructuring the SARS like corona virus found in bats. She became figure of controversy since the pandemic. This is due to her paper

published in 2015 wherein she discussed her own research into synthetic viruses. She has now given an interview to *Caixin*, a media outlet with close ties with communist party and rejected all allegations from world. Since the first SARS outbreak in 2002-03, Dr. Shi Zhengli and her team have been conducting research on corona virus. Since 2010 onwards, the focus of her team was redirected to identify the capacity of corona virus transmission across species specifically putting spotlight on S-protein of corona virus, in short possible transmission into humans. In June 2010, Dr. Shi Zhengli and her team published a paper entitled "*Angiotensin converting enzyme 2 (ACE 2) proteins from different bat species confer variable susceptibility to SARS-CoV entry*" which demonstrated their awareness of special relationship between S-protein and ACE-tool receptor. It also indicates that Dr. Shi Zhengli had unearthed the passageway for corona virus into human bodies. In October 2013, she and her team published another paper entitled "*Isolation and characterization of a bat SARS like corona virus that uses ACE-2 receptor"*. In this paper they demonstrated the direct human to human infection of SARS like viruses to humans without the need of intermediate host. In November 2015 she and her team published paper in journal , '*Nature Medicine*' in which they discussed creation of synthetic viruses. In this paper they have discussed creation of synthetic virus, a self-replicating virus which has SARS-like framework with S-protein replaced by one they found in bat corona virus mentioned in the 2013 paper. This new virus demonstrated a powerful ability for cross-species infection. Mice which was infected with synthetic virus revealed serious lung damage with no cure. This symbolized Dr. Shi Zhengli's successful splicing of the SARS virus was a key to open the doors to the cross-species transmission. Although she did not conclude any results but her move to research on primates suggest that this was move to closely simulate the infection of humans with this new synthetic virus.

Her experiments quickly triggered widespread debates within academic community across the globe. Simon Wain-Hobson, a virologist at the Pasteur Institute in Paris pointed out that the researchers have created a novel virus that grows remarkably well in human cells and if the virus escaped, nobody could predict the trajectory. On November 14, 2018; Dr Shi Zhengli spoke at School of Life Sciences and Biotechnology at Shanghai Jiatong University.The topic was *"Studies on Bat corona virus and its cross-species infection*". Reports of this event has since been deleted from the University website. In October 2014, the Obama administration had suspended funding of SARS, MERS and similar research considering the potential threats. The funding pause included Dr. Shi Zhengli's research project '*Genetic engineering of SARS like corona virus in bats'* , a collaborative effort with University of North Carolina. After Wuhan outbreak, Indian researchers compared protein sequence between 2019-nCoV and SARS. They discovered 2019 nCoV had four new sequences inserted, all of which can be found in HIV in paper entitled "*Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1, gp120 and Gag*." Afterwards, Dr. Shi Zhengli discredited the doubts raised by experts but never denied the existence of four inserted sequences. The scientist from Gene bank found that there are only three viruses in globe which contains all these sequences i.e. HIV, bat corona virus discovered by Dr. Shi Zhengli and third is new Wuhan corona virus. The research direction of Dr. Shi Zhengli attracted wide criticism, as to why she was working on corona virus that can infect humans, whether it was meant for bioweapon or to create a vaccine to gain profit from globe.

However, we need extensive research and investigation within China to solve this mystery which seems impossible considering Chinese regimes potential cover up.

THE WUHAN P4 LABORATORY

Amidst the speculation that Wuhan corona virus is generated by reverse engineering, Dr. Shi Zhengli published paper on February 3, entitled "*A pneumonia outbreak associated with a new corona virus of probable bat origin*". In this paper, they confirmed that 2019 nCoV uses the same cell entry receptor- angiotensin converting enzyme (ACE-2) as SARS-CoV. She also announced 2019-nCoV genome sequence was 96.2 % consistent with bat corona virus originating in Yunnan province called RaTG 13 signaling a natural source of Wuhan virus. However, the claims made by Dr. Shi Zhengli are doubtful because the outbreak occurred in Wuhan, the same location is the P4 lab in which she was based and the lab has housed highly similar viruses. By considering the natural response, the authorities should have inspected the laboratory for identifying potential leakage however they diverted public attention from P4 laboratory to 'Huanan Seafood Market' which sells no bats and designated it as origin of outbreak. At the same time authorities sealed all virus samples, prevented international experts from joining the investigation and used national television to suppress the whistleblowers like Dr Le Wengliang who tried to disclose the outbreak. If the Wuhan virus occurred naturally then why the government did censor relevant information and blocked investigation? Does the Wuhan P4 laboratory have some secrets to hide? Gordon Chang, a columnist and Asian affairs expert suggested that we should consider theory of lab origin until we don't know anything about source of outbreak. After the outbreak, Wuhan Institute of Virology kept strange silence. Under normal circumstances being the best virology institute in country it should have been the first one to actively respond when entire country was fighting against pandemic. Here it should be noted that Wuhan Institute of Virology displayed series of abnormal events from the beginning of 2020.

On January 2, the Director General of Institute sent an email to all internal staff regarding the strict prohibition of disclosure of any information related to Wuhan unknown pneumonia. An email clearly stated that National Health Commission mandates all detection, data, results and conclusion related to this outbreak cannot be published on self-media or any other media including (State media). On January 21, a new drug 'Remdesivir' for treatment was patented by Wuhan Institute of Virology. On February 3, Dr. Wu Xiahua blew the whistle using his real name that Dr. Shi Zhengli and laboratory management might have led the Wuhan virus to leak from the lab. On February 4, Chairman of Duoyi, Xu Bo blew the whistle using real name that the Wuhan Institute of Virology was suspected of manufacturing and leaking this virus i.e. the Wuhan corona virus. On February 7, a top biochemical weapon expert of People's Liberation Army, Chen Wei officially assumed control over Wuhan Institute of Virology's P4 lab. On February 14, Chinese President Xi Jinping called for the inclusion of biosecurity into China's national security framework and to accelerate the introduction of biosecurity law. On February 15, the institute refuted widely spread rumors on Chinese social media that female graduate Huang Yangling was patient zero and perished. However Huang's photo, CV and thesis were all removed from institute's official website leaving only her name. On February 17, an institute researcher, Chen Quanjiao blew the whistle using her real name that

the Director General of Institute Wang Yanyi was suspected of leaking the virus. The keywords like leakage of virus, a biochemical weapon expert assumes command over an institute and biosecurity law gives strong feeling that P4 laboratory is not an ordinary lab.

On January 23, the day when Wuhan was lockdowned, a French website "*Challenge*" published one article which revealed many details about collaboration between France and China to establish P4 laboratory in Wuhan. In 2002-03 after SARS outbreak in China, the Chinese Academy of Sciences requested assistance from French government to build virology research center of high standards and agreement was signed between two governments. According to the contract, French architect was responsible for engineering and constructing the laboratory. However, the Chinese authorities handed over the work to the local Wuhan architect company IPPR which has close ties with subsidiaries of People's Liberation Army. Knowing all these the French government delayed work repeatedly and tactically tried to halt the work. It was in 2017, the Wuhan P4 laboratory became operational. French security continues to suspect that Chinese regime is conducting biochemical weapon experiments. Considering all these, the question arises here that who really is in control of Wuhan P4 laboratory.

The P4 laboratory is subsidiary of Wuhan Institute of Virology under the Chinese Academy of Sciences. The director of P4 lab is Yuan Zhiming who is also head of the Chinese Academy of Sciences. He was also in-charge for designing and funding of constructional responsibilities of institute under ex-Vice President of academy "*Jiang Mianheng*" from 1999 to 2011. Jiang Mianheng is eldest son of the Chinese Communist Party's leader , Jiang Zemin who served as the President of People's Republic of China from 1993 to 2003. Following the Tiananmen massacre, he ousted many senior leaders of Chinese Communist Party (CCP) before assuming Presidency. He sent his eldest son Jian Mianheng to Chinese Academy of Sciences where he created many institutes such as Shanghai Institute of Life Sciences, colleges and universities, Shanghai hospitals, Military hospitals and Military Research Institute. In this period, he controlled major life sciences project and allocated major funding for research. Jian Zhicheng, son of Jiang Mianheng is controlling share in Wuxi Apptec. Company which controls Fosun pharmaceuticals, China's agent for 'Remdesivir'. In 1999, when Jiang Zemin was in power, the People's Liberation Army (PLA) published book , '*Unrestricted War'* in which strategy for weaker nation to combat stronger nation are discussed. The new strategy called 'unrestricted warfare' includes interalia various tactics such as military assault, guerrilla warfare, terrorism, bioweapon, drug trafficking, environmental destruction and computer virus dissemination. In 2015, an Israeli expert and formal intelligence officer Dany Shoham published paper in *Indian Journal of Defense Studies* which discussed about China's biological program in details. In this paper he pointed out 12 facilities affiliated with defense establishment, 30 facilities associated with People's Liberation Army that are involved in research, development, production, testing and storage of biological weapon. Federation of American Scientist indicated similar concern in their evaluation reports. The organization believes the Chinese regime possess: several biological warfare programs including research and development, manufacturing and weaponizing capability. That's why many experts around the globe believe that the long-term planning of Chinese regime is to dominate on global stage by achieving these capabilities. Many experts

believe that global community should understand this doctrine and essential measures should be taken to stop this, otherwise thing can go out of control.

CONCLUSION

At Present the Corona virus pandemic has spread to 200 + countries with no sign to slow down. The United States has announced state of national emergency, Europe became the new epicenter of pandemic, tragic scenes previously seen in Hollywood movies are now playing out live at world stage. The role played by the World Health Organization (WHO) during the pandemic is doubtful. Initially, WHO refused to endorse human-to-human transmission of corona virus following instructions from the Chinese Regime and later on, it accepted human-to-human transmission. During the outbreak many countries such as USA, India etc. barred entry of flights from China, WHO got riled up and condemned this move. Till the time, it acknowledged inter-species transmission, the virus already spread to many countries. US President was exasperated by these and launched several attacks against the WHO and even threatened to halt funding. Finally, on 14th April 2020 he announced that his administration had stopped funding of WHO. Many world leaders and experts were shocked by this move in the middle of global corona virus pandemic. On 17th April, Trump tweeted and accused WHO of ignoring email sent by Taiwan authorities in December in which they had warned that corona virus could be transmitted in humans.

The WHO could have played active role to contain this pandemic but it has failed. Under mounting global pressure, China has relented its opposition and backed EU draft resolution tabled at the World Health Assembly (WHA). The WHA is a decision-making body of the Geneva-based World Health Organization which held virtual meeting on May 18 which was attended by all member-states and the resolution was passed. On the issue of the origin of the virus, all parties agreed to work in close collaboration with WHO for animal health and Food and Agricultural Organization with purpose to reduce future infections. In addition to that, all parties agreed that WHO should conduct an assessment over its response to Covid-19 with consensus also been reached about evaluating the role of WHO which came under sharp criticism of the US President Donald Trump. The customary practice of consultation between Director General and member-states to review lesson learnt and proposed suggestions for future was done. In the consultations vast majority agreed that the pandemic is not over yet and co-operation to fight against the pandemic is most urgent task. China agreed that all parties would enhance co-operation and engage in constructive dialogue in improving the public health. On the other hand, China pretends to be responsible member to the international community but in reality, they tried to cover up and allowed the virus to spread to create 'global pandemic'. On March 24, a Texas lawyer, Larry Klayman filed a complaint in federal court seeking at least $ 20 trillion from Chinese government and asked to pay dearly. On April 14, 2020 British Think Tank "Henry Jackson Society" advocated compensation of 351 billion pounds from the Chinese Communist Party to United Kingdom. On the same day, the All India Bar Association filed a complaint to the United Nations Human Rights Council seeking an unspecified amount of reparations from China over global spread of corona virus. The global corona virus pandemic has affected world economy badly with almost all major economies being under nation-wide lockdown. The United Nations has warned that the global economy

could shrink by 1% which is much less than previous forecast of 2.5 %. It is also said that it could be even worse if restrictions on economic activities would extend without proper fiscal responses. Evidently Chinese regime has violated the international health regulations and international community might take action against Chinese regime, as many experts suggest. US President Donald Trump has also indicated that he would be taking action against China during one of his daily press briefing at the White house. Whether it could be economic or other sanctions, has not yet been stated with clarity.

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ABNORMALITIES OF BLOOD CIRCULATION THROUGH NARROWED ARTERY IN THE EXISTENCE OF SOME PARAMETERS

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ABSTRACT

A mathematical replica and finite difference scheme were introduced to solve the governing equations in the conditions of vorticity-stream function. The replica predictions are agreed with results. It is seen that the mathematical values of Hematocrit, Reynolds, Magnetic Reynolds number, as well as the pressure gradient varies. A numerical calculation can be written for the considerable evaluation of axial velocity in the progressive region along with analytical result for 0.5 to 4. Steady movement of development of axial velocity takes place at a different axial situation in the presence of magnetic field, when Reynolds number lies between 0 to 10.

Keywords: Fluid Flow Characteristics, Hematocrit Value, Magnetic Field ,Pressure Gradient.

INTRODUCTION

Arteries throughout the body of a living being may be subjected to hardening, which causes symptoms of several diseases as hardened pipes cannot lead enough blood to the creature's body. Narrowing or hardening of the blood pipes may lead to the heart attack. A series of steady movement *in vitro* experiments are mentioned by Young *et al*. (1973). They described some major hydrodynamic factors with pressure drop, separation, and turbulence. An approximate result is presented by Morgan and Young (1974) to the solution of incompressible movement through an axi-symmetric constriction. The mathematical geometry is intended to replicate

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arterial stenosis, and the result is applicable to both mild as well as severe stenosis for Reynolds numbers less than transition. Chakravarty (1987) has done an analytical work to examine the result of stenosis on vascular deformability and the movement of liquid in a tube by employing a proper mathematical representation. The artery is assumed to behave here as an originally stressed elastic cylindrical vessel having a non-Newtonian thick incompressible liquid. Huang *et al* (1995). has investigated flow in a tube with an occlusion. The results are mentioned in the context of blood movement in stenosed arteries. Mathematical results for steady and pulsatile movements confirm, that elevated shear stress is not possible to start atherosclerosis lesions. Chakravarty *et al*. (2000) have dealt with pulsatile movement characteristics of liquid in a distensible bifurcated tube having stenosis when it is concerned with full-body acceleration. Hemodynamic properties of blood movement through arterial stenosis are numerically examined by Moayeri *et al*. (2003). Blood is taken as a Newtonian liquid and the pulsatile nature of the movement is modeled by measured values of the movement rate and pressure for canine femoral artery. The micro polar representation for axi-symmetric liquid movement through an axially non-symmetrical but symmetric mild narrowed tapered artery has been studied by Mekheimer *et al.* (2008). To estimate the consequence of the stenosis, an appropriate geometry has been measured. The axial figure of the stenosis can be changed simply by changing a parameter. A numerical model for blood movement in the existence of a magnetic field is investigated by Bali (2011). Mathematical investigation of blood movement through an artery with many stenoses in the occurrence of a catheter has been investigated by Srikanth (2012). The nonlinear equations are used to resolve the velocity as well as micro-rotation mechanism in the conditions of Bessel functions. Shit, G. C. (2013) has investigated blood flow behavior and its properties in the presence of magnetic field. Mathur *et al*. (2013) have developed a mathematical representation for studying the non-Newtonian flow of blood through a stenosis arterial section. Power-law liquid represents the non-Newtonian nature of blood. The hemodynamic actions of the blood movement are influenced by the existence of the arterial stenosis. Analytical study of MHD blood movement in an absorbent inclined stenosis tube under the inclined magnetic field has been studied by Srivastava (2014). The blood movement in the arterial system has been considered as a liquid dynamics problem by Blessy *et al*. (2016). Simulation of blood movement in the arterial system provides a better physiology of the human body. Jamalabadi (2016) has focused on transient modeling of blood movement through a tapered artery surrounded by solenoid under the occurrence of heat transfer. The oxygenated as well as deoxygenated blood is considered the Newtonian and non-Newtonian fluid. According to Siddiqui (2017), blood can be understood as a suspension of magnetic particles, due to the occurrence of hemoglobin in blood cells. The hemodynamic as well as rheological characteristics of blood could assist us to identify and perceive the pathological circumstances of stenosis.

DEFINING THE PROBLEM

Reynold Number

Reynolds number was described by Reynolds in 1883. The Reynolds number is used to categorize the fluids systems in which the effect of viscosity is important in controlling flow pattern of a fluid. Reynolds number (N_{Re}) is defined as the ratio of fluid momentum force to viscous shear force. Mathematically, the Reynolds number, N_{Re}, is calculated by dividing the sum total of multiplication of density, velocity and diameter by viscosity. As per API 13D recommendations, it is assumed that a Reynolds number less than or equal to 2100 indicates laminar flow, and a Reynolds number greater than 2100 indicates turbulent flow.

Formulation of the solution

$$u\frac{\partial u}{\partial r}+w\frac{\partial u}{\partial z}=\frac{1}{\rho_0}\left[-\frac{\partial p}{\partial r}+\frac{\partial}{\partial r}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(ru\mu(r)\right)\right]\right]+\frac{\partial}{\partial z}\left[\mu(r)\frac{\partial u}{\partial r}\right] \tag{1}$$

$$u\frac{\partial w}{\partial r}+w\frac{\partial w}{\partial z}=\frac{1}{\rho_0}\left[-\frac{\partial p}{\partial z}+\frac{1}{r}\frac{\partial}{\partial r}\left[\left(ru\mu(r)\frac{\partial w}{\partial r}\right)\right]\right]+\frac{\partial}{\partial z}\left[\mu(r)\frac{\partial w}{\partial z}\right]-\beta_0{}^2\lambda w \tag{2}$$

$$\text{And } \frac{1}{r}\frac{\partial}{\partial r}(\boldsymbol{u}\ )+\frac{\partial w}{\partial z}=0 \tag{3}$$

Here, inertia terms are ignored and the magnitude of velocity in r – axe, u is very less in comparison to magnitude of velocity (w) in z-direction (i.e. u<<w) and the variation of the velocity gradient into z-axe is minimum than velocity gradient into r-axe, therefore, equations (1) as well as (2) are reduced as follow:

$$-\frac{1}{\rho_0}\frac{\partial p}{\partial r}=0 \tag{4}$$

$$\frac{\partial p}{\partial z}+\frac{1}{r}\frac{\partial}{\partial r}\left[\left(-r\mu(r)\frac{dw}{dr}\right)\right]+\beta_0{}^2\lambda w=0 \tag{5}$$

Thus, the equation of movement written in equation (5), for the steady as well as the axially symmetric movement of blood through an artery provided with manifold mild stenosis as well as magnetic area, under the described assumption is transformed as:

$$\frac{dp}{dz}+\frac{1}{r}\frac{\partial}{\partial r}\left(-r\mu(\mathrm{r})\frac{dw}{dr}\right)+\beta_0{}^2\lambda w=0 \tag{6}$$

The connection between the magnetic field and maximum Hematocrit is given as

$$h(\mathrm{r})=H\left[1-\left(\frac{r}{R_0}\right)^K\right] \tag{7}$$

Here k≥2 is a bound factor which determined the shape of Hematocrit profile.

This shape is given by equation (7) and applicable for a very dilute suspension of red units which are considered spherical in profile.

The boundary circumstances are:

$$\frac{\partial w}{\partial r} = 0 \qquad : r = 0 \tag{8}$$

$$w = 0 \qquad : r = R(z) \tag{9}$$

The specified dynamical equation for the blood fluid flow in cylindrical method is

$$\rho_0 \frac{\partial u}{\partial t} = -\frac{\partial p}{\partial z} - \frac{1}{r}\frac{\partial (r\tau)}{\partial r} + G(\mathrm{t}) + \mu_0 H \frac{\partial M}{\partial z} \tag{10}$$

the volumetric blood flow rate Q (t) is

$$Q = \int_0^{\frac{R}{R_0}} 2\pi R_0 x w(x) dx \tag{11}$$

Let Q_0 denotes the flow rate of plasma fluid in unconstructed tube when M=0, H=0.Then

$$Q_0 = \frac{\pi R_0^{\,3}}{8\mu_0}\left(\frac{dp}{dz}\right)_0 \tag{12}$$

Where $\left(\frac{dp}{dz}\right)_0$ denotes pressure gradient of flow in the normal tube in absence of magnetic field

Thus, non-dimensional flow rate $\bar{Q} = \frac{Q}{Q_0}$ is

$$\bar{Q} = \frac{G\left(\frac{R}{R_0}\right)^4}{G_0\left(a_1 + \frac{M^2}{4}\left(\frac{R}{R_0}\right)^2\right)} \tag{13}$$

Where

$$R = \frac{.25\,\mathrm{Re}}{1 + 0.023Ha + 0.026Ha^2 - 0.0015Ha^3} \tag{14}$$

RESULT & DISCUSSION

In this study, the mathematical values of Hematocrit value, Reynolds, Magnetic Reynolds number, as well as the viscosity, vary between 0 to 10. For hemodynamical movements in the aorta, it lies between 0 to 2. With an objective to get the accuracy of our mathematical results, the comparison has been done for steady phenomena in the developed world.

Figure 1 depicts how flow rate of plasma is augmented with increased viscosity as well as radius of artery. In the Figure 2 , it is seen that non- dimensional flow rate is augmented with increased radius of artery as well as pressure gradient. Figure 3 shows the mathematical calculation of length of artery at different hematocrit value as well as different Reynolds number.

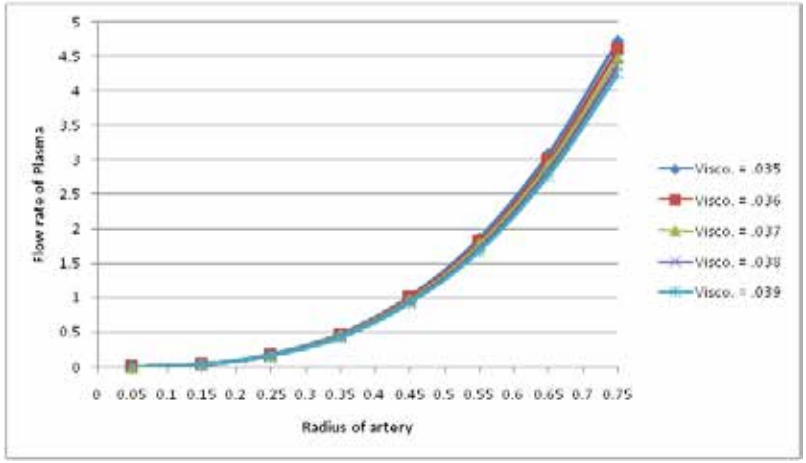

Figure 1: Variation of flow rate of Plasma at different viscosity

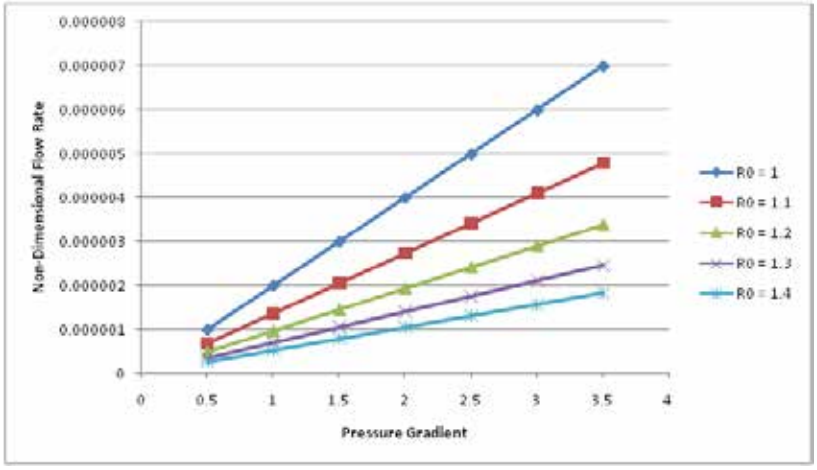

Figure 2:Variation of Non - Dimensional flow rate at different artery radius

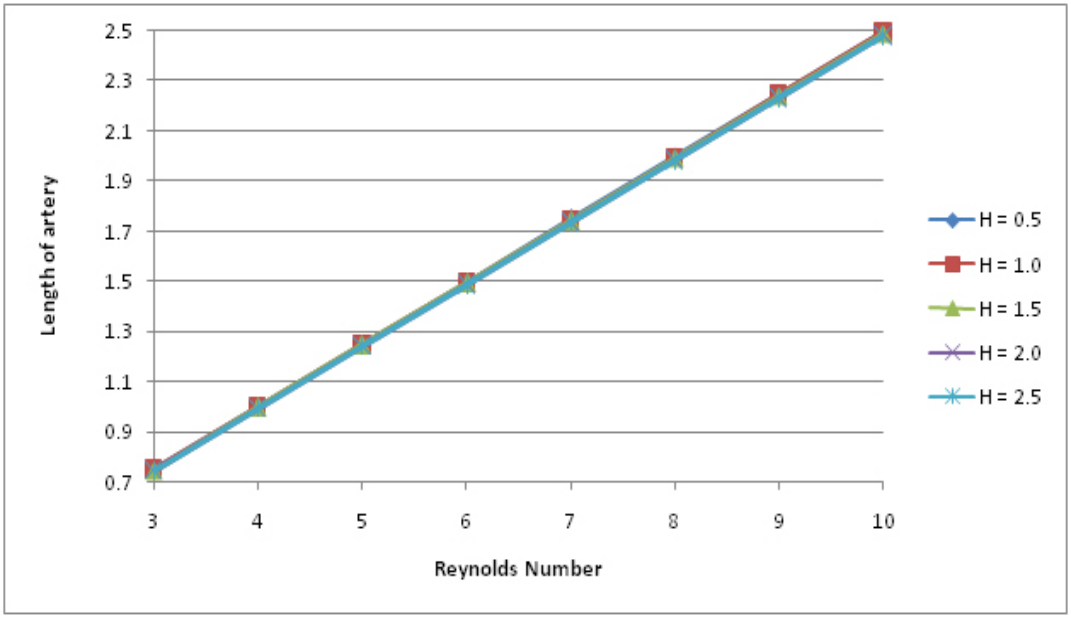

Figure 3: Variation of length of artery at different Hematocrit value

CONCLUSION

The steady entrance magnitude in the presence of magnetic strength, as well as the Reynolds number (Re), can be approximated in theory. During the pulsatile blood movement, the reversal movement can be suppressed by applying a strong magnetic field. The Womersley parameter has reducing cause on velocity in the main region and an enhancing consequence in the boundary coat during its peak movement, while the system is reciprocal in the minimal movement rate. Therefore, the study says about major physiological phenomena as well as provides proper information to the researchers who are having interest in simulation of cardiovascular movement. It is further concluded that finding the solutions with the interaction of a magnetic field in an unsteady system is not possible except numerical simulation.

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SYNTHETIC ROUTES, CHARACTERIZATION AND BIOLOGICAL SIGNIFICANCE OF 1, 2, 4-TRIAZINE DERIVATIVES:COMPREHENSIVE REVIEW

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ABSTRACT

When the three carbon-hydrogen units are replaced by three nitrogen atoms in a six-membered heterocyclic ring system homologous to benzene ring system,this system of compounds are called as triazines.$C_3H_3N_3$ is the general formula of triazines. Triazines are known to have three isomeric forms, depending on position of which of the carbon atoms of benzene ring is being replaced by the nitrogen unit.1,2,4-Triazine heterocyclic compounds as well as its derivatives are known to possess a wide variety of applications such as anti-viral, anti-HIV, anti-hypertensive, analgesic, anti-cancer, cyclin-dependent kinase inhibitors, anti-inflammatory, anti-malarial, cardiotonic and estrogen receptor modulators. They also possess properties like lubricants, analytical reagents as well as dyes. This paper reviews the literature on biological potential of 1,2,4-triazine derivatives.

Keywords: Dyes, Heterocyclic, Inhibitors,Isomeric,Reagents,Triazines.

INTRODUCTION

Heterocyclic Chemistry is one of the most important and significant part of the chemistry. The scientific discipline at the intersection of chemistry and pharmacy including designing, synthesizing and development of pharmaceutical drugs. Heterocyclic compounds (five, six and seven members) have special applications in the field of synthetic organic chemistry and

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biological activity. More than eighty percent of the medicines possess heterocyclic nucleus in their structure. Majority of natural products particularly alkaloids, which are being used as medicines with the development of civilization for mankind and other living things, have heterocyclic moieties as their constituents. Derivatives1-10of pyrazole, Imidazole, pyrimidine, thiadiazole, pyridine, thiazole, quinolineetc, are very important synthons for drug designing and also in the field of synthetic medicines.

These heterocyclic systems possess various pharmacological activities viz., analgesic, anti-tumor, anti-viral, anti-cancer, anti-bacterial, anti-parasitic, anti-malarial, anti-radiation, anti-neoplastic, and anti-hypertensive etc. The triazine structure is a heterocyclic ring homologous to six membered benzene ring in which three carbon atoms are replaced by three nitrogen atoms. The difference in the position of three nitrogen atoms distinguish the isomers of triazine which are referred to as,1,2,3-triazine heterocyclic,1,2,4-triazine heterocyclic and 1,3,5-triazine heterocyclic molecules [1]

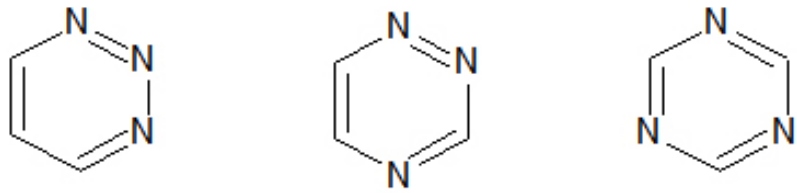
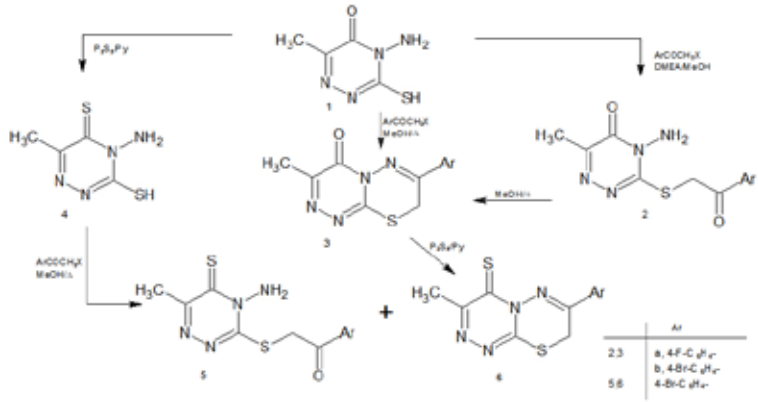


Figure 1: Three Heterocyclic N -atoms

From the past few years, the interest in synthesizing heterocyclic compounds containing, 1,2,4-triazine ring is increasing day by day because of their significance in biological problems.1,2,4-triazine molecule is a heterocyclic molecule analogous to benzene in which three carbon atoms are replaced by three nitrogen atoms. In recent years, there has been increasing interest in the synthesis of heterocyclic compounds containing a 1,2,4-triazine ring because of their biological significance. Several 1,2,4-triazine derivatives have been demonstrated to be of herbicidal, anti-hypertensive, anti-viral activity as well as activity against *Staphylococcus aureus, Bacillus cereus* and P388 Lymphocytic leukemia.1,2,4-triazines are regarded as 6-aza being analogues to pyrimidine bases, needless to say that pyrimidine, in general, have a great biological importance. Further 1,2,4-triazine derivatives have been reported to possess biological activities including against tuberculosis, analgesic, anti-hypertensive, anti-HIV, anti-viral, cyclin-dependent kinase inhibitors, anti-parasitic,neuroleptic, anti-inflammatory,anti-hy pertensive,analgesic,cardiotonic,anti-malarial [2-22].

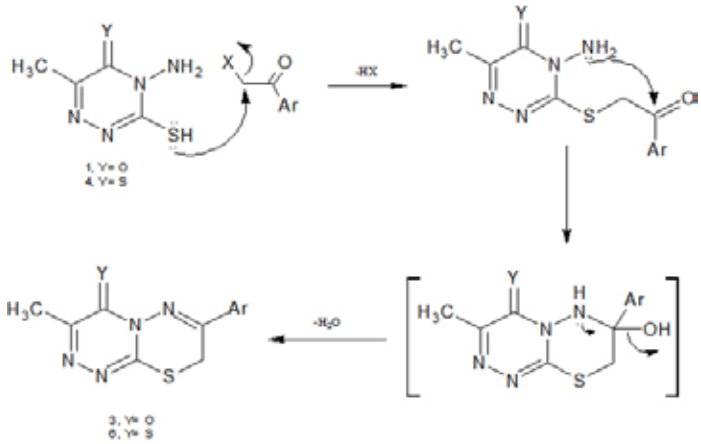
TRIAZINE DERIVATIVES AND THEIR BIOLOGICAL APPLICATION;

The reaction between thiocarbohydrazide with pyruvic acid results in the formation of 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one (2) according to Dornow*et. al*.[38]. The condensation reaction between 2-phenyl-4-(4-floro benzylidene)-1,3-oxazol-5-one and hydrazine hydrate, semicarbazide and thiosemicarbazide then followed by cyclization with the removal of water molecule results in the formation of 2,3,5-trisubstituted-1,2,4-triazine-6-one[23].



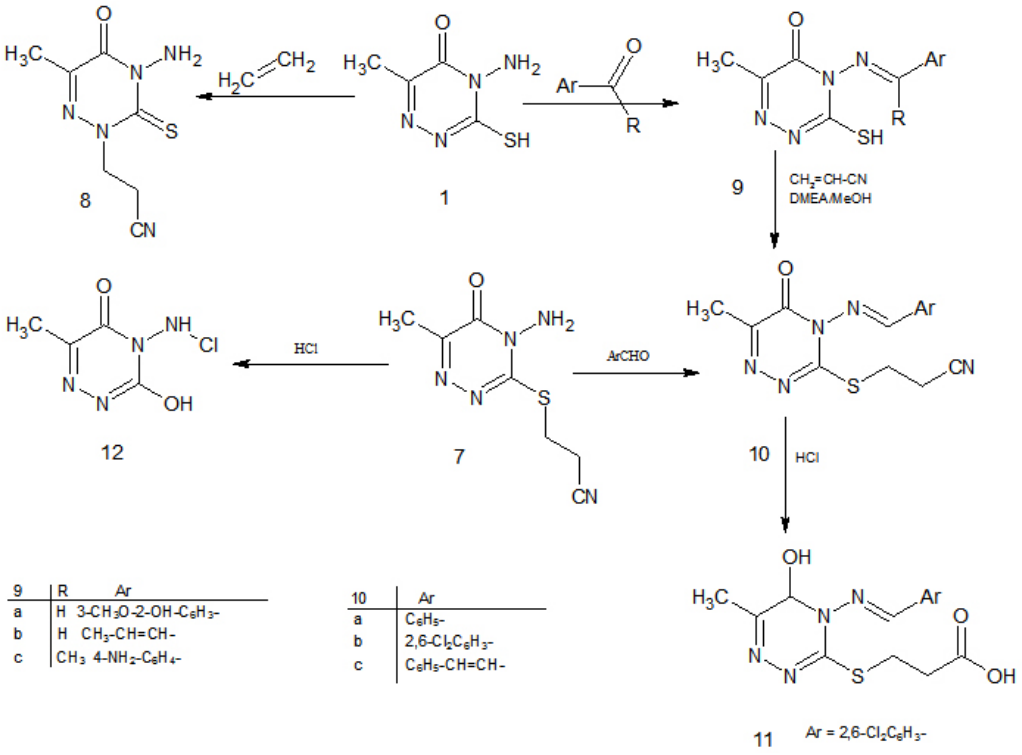
SCHEME 1

Treatment of (1)with 4-fluolophenacyl chloride and/or 4-bromophenacyl bromide in methanol at room temperature in the presence of N,N-dimethylethylamine (DMEA)afforded high yields of the corresponding phenacylthio derivatives 2a,b which were cyclized to 8H-7-aryl-3-methyl-as-triazino [3,4-1b], 3[4] thiadiazin-4-ones (3a,b) by heating in methanol for one hour. Compounds 3a, bwere also obtained via the reaction of 1 with phenacyl halides in boiling methanol. Thiation of compound (1)with phosphorus pentasulfide in boiling anhydrous pyridine afforded 4-amino-3-mercapto-6-methyl-1,2,4-triazine-5(4H)-thione (3),in 63 % yield. Treatment of compound 4 with 4-bromophenacyl bromide in boiling methanol yielded a separable mixture of 4-amino-3-(4-bromophenacyl)thio-6-methyl-2,4-triazine-5(4H)-thione(4) and 8H-7-(4-bromophenyl)-3-methyl-as-triazino[3,4-bI], 3[4] thiadiazine- 4-thione (6) in 65 % total yield, which on further heating for 2 hrs.,gave (6)as a sole product in 60 % yield. Compounds (5)and (6)were separated from the mixture by treatment with boiling dilute acetic acid that dissolved (5). Compound (6)was obtained by another pathway when 3b was treated with phosphorus pentasufide in boiling anhydrous pyridine (Scheme 1).



SCHEME 2

Isolation of the phenacylthio derivatives 2a, b and (5), at different reaction conditions, suggests a mechanism for formation of the triazino [3,4-b] [1,3,4] thiadiazines3a,b and compound (6). In such mechanism, a nucleophilic attack of the phenacyl halides occurs by the mercapto group to give the S-alkylated products 2a,b and compound (5); and then an internal nucleophilic attack by the NH_2 group on the CO takes place with a loss of a H_2O molecule to afford the final products (3) and (6) (Scheme 2).



SCHEME 3

Compound (7) was condensed with benzaldehyde, 2,6-dichlorobenzaldehyde and cinnamaldehyde in methanol to afford the corresponding arylideneamino derivatives 10a-c in 72-84% yields. Condensation of compound(1)with vanillin, crotonaldehyde and 4-aminoacetophenone gave the corresponding anils9a-c in 60-82 % yields. In case of the condensation reaction with crotonaldehyde or cinnamaldehyde, an inseparable mixture of *Z'E* isomers was obtained in 1:4 ratio (according to ^{13}C NMR). 4-(2,6-Dichlorobenzylidene) amino-3-(2-cyanoethyl)thio-6-methyl- 1,2,4-triazin-5(4H)-one (10b) was also obtained in 73% yield when 9 (Ar= 2,6-$C_{12}C_6H$,-)'6 was treated with acrylonitrile in boiling methanol in the presence of DMEA. Acid hydrolysis of 10b afforded the corresponding acid 11 in 51 % yield, while compound 7, under the same reaction conditions, gave 4-amino-3-hydroxy-1,2,4-triazin-5(4H)-one as a hydrochloride salt (12) in 38 % yield (Scheme 3).

The structures of the newly synthesized compounds were confirmed by analytical data, IR, 'H NMR, ^{13}C NMR and mass spectra.

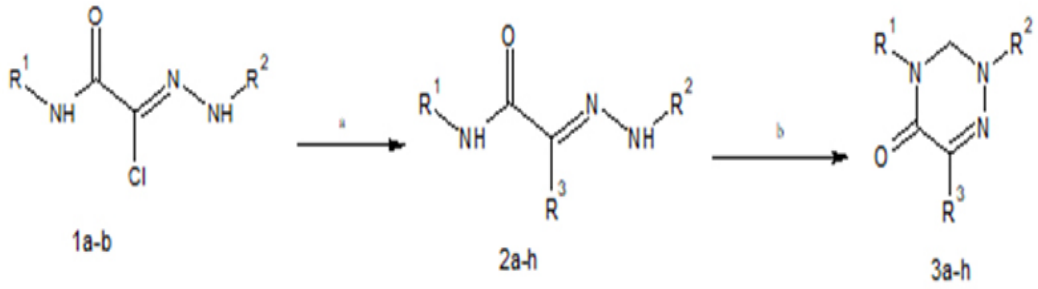
In this literature review this has been found that standard disc method was adopted for testing the anti-microbial activity of the compounds 2a, 3a,4,5,7,9a, 10b and 11. Filter paper discs were moistened with the tested compound solution in dimethylsulphoxide of specific concentration 1 mg/disc and carefully placed on agar culture plates that have been previously inoculated separately with the microorganisms; *Aspergillus niger, Aspergillus flaws, Aspergillus fumigatus, Penicillium notatum, Candida albicans* and *Staphyllococus saureus.* After incubation, the diameter of the growth inhibition around the disc was measured. Compounds 2a, 4, 5 and 11 were found to be active against *A. fumigatus, C. albicans and S. aureus;* compounds 2a, 4 and 11 showed activity against *P.notatum*; compounds (4)and (5) showed activity against *A. niger* while, no compound(s) was found to possess marked activity against A. *flavus* (Table 1).

Table 1: Diameters of the Inhibition Zones (mm) Exhibited by the Tested Compounds

No.	*A. niger*	*A. flavus*	*A. fumigatus*	*P. notatum*	*C. albicans*	*S. aureus*
2a	-	-	11	6	17	5
3a	-	-	-	-	-	-
4	12	-	17	13	15	26
5	19	-	12	-	21	7
7	-	-	-	-	-	-
9a	-	-	-	-	-	-
10b	-	-	-	-	-	-
11	-	-	9	5	12	4

A number of small molecules possessing 1,2,4-triazine scaffold have been shown to exhibit a great variety of pharmacological effects, from last few years. On the application of these compounds, such as 5-lipoxygenase (5-LO) inhibitors, herbicides, bactericides, fungicides, antimicrobials, and gonadotropin-releasing hormone receptor (GnRH-R) antagonists ,several reports have been published. Even for fused 1,2,4-triazine compounds, not only anti-tumor and anti-metastatic activities against a wide range of cancer cells but also kinase inhibiting activities could be observed.

In 2007, cancer accounted for 7.9 million death cases (around 13% of all deaths). Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. Heterocyclic compounds containing an amidrazone scaffold, novel 1,2,4-triazines as efficient anti-cancer drugs with low cytotoxicity and good bioavailability properties were synthesized. The straightforward synthesis of eight 1,2,4-triazin-5-ones 3a–h is represented in Scheme 4.



1a:	R^2=C_6H_5	**2a, 3a:**	R^2=C_6H_5; R^3=$(CH_3)_2N$	**2e, 3e:**	R^2=C_6H_5; R^3= piperidine
1b:	R^2=4-Cl-C_6H_4	**2b, 3b:**	R^2=4-Cl-C_6H_4; R^3=$(CH_3)_2N$	**2f, 3f:**	R^2=4-Cl-C_6H_4; R^3=piperidine
		2c, 3c:	R^2=C_6H_5; R^3=pyrrolidine	**2g, 3g:**	R^2= C_6H_5; R^3=morpholine
1-3:	R^1=2-Cl-C_6H_4	**2d, 3d:**	R^2=4-Cl-C_6H_4; R^3=pyrrolidine	**2h, 3h:**	R^2=4-Cl-C_6H_4; R^3=morpholine

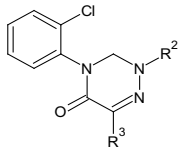
Scheme 1. Reagents and conditions: (a) dimethylamine for **2a-b,** pyrrolidine for **2c-d**, piperidine for **2e-f**, morpholine for **2g-h,** dioxane, room temperature, 12 h and (b) H_2CO, TsOH, EtOH, 1-2h, reflux.

SCHEME 4

Hydrazonoyl chlorides 1a–b as starting compounds for triazinone synthesis was prepared according to known literature procedures. Conversion of 1a–b with the respective amines in dioxane led to amidrazone intermediates 2a–h. One to two hours of refluxing 2a–h with formaldehyde in the presence of p-toluen-sulfonic acid yielded nearly pure 1,2,4-triazin-5-ones. 3a–h of refluxing 2a–h with formaldehyde in the presence of p-toluen sulfonic acid yielded nearly pure 1,2,4-triazin-5-ones 3a–h (Scheme 1).

Among the eight1,2,4-triazin-5-ones synthesized, 3a–d showed the highest anti-proliferative effect on the human leukemia cell line K-562 with a moderate growth inhibition efficacy on the human umbilical vein endothelial cell line (HUVEC). Though the most potent compound 3c is obviously less active against K-562 than Imatinib, the preferred drug for treating chronic myeloid leukemia (CML), a comparable low growth inhibiting effect on HUVEC was found. Cytotoxicity of 3c against HeLa cells is ranging at similar values. In contrast to doxorubicin, an established but highly cytotoxic drug for the treatment of acute myeloid leukemia (AML), lymphoma, sarcoma, and carcinoma, 3c showed a five times lower anti-proliferative activity against K-562, but a 22 times lower cytotoxicity on HeLa cells (Table 2).

Table 2: Substitution Patterns, Lipsinki's 'Rule-of-Five' descriptors, experimental log P values (Log P_{exp})

	R^2	R^3	Mw^2	nON^2	$nOHNH^2$	Log P_{cak} [a]	logP_{exp}
3a	C_6H_5	$N(CH_3)_2$	328.80	5	0	3.5	3.6
3b	4-Cl-C_6H_4	$N(CH_3)_2$	363.25	5	0	4.2	4.2
3c	C_6H_5	Pyrrolidine	354.84	5	0	3.9	4.0
3d	4-Cl-C_6H_4	Pyrrolidine	389.29	5	0	4.6	4.6
3e	C_6H_5	Piperidine	368.87	5	0	4.4	4.6
3f	4-Cl-C_6H_4	Piperidine	403.31	5	0	5.1	5.0
3g	C_6H_5	Morpholine	370.84	6	0	3.3	3.5
3h	4-Cl-C_6H_4	Morpholine	405.28	6	0	4.0	4.0
Imatinib	-	-	493.62	8	2	3.9	1.22[22]
Doxorubicin	-	-	543.52	12	7	0.57	0.71[23]

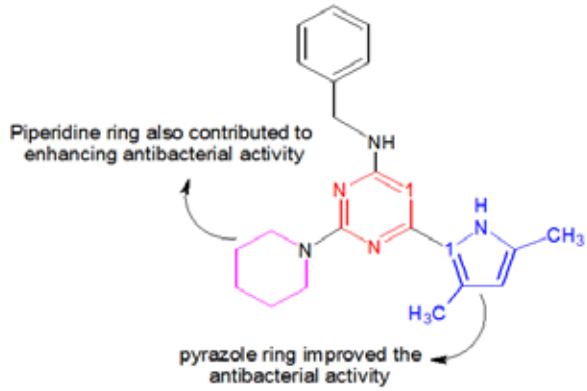
n.d.: not determined.[a]Lipsinki descriptors: Mw, molecular weight; nON, number of hydrogen acceptors; nOHNH, number of hydrogen donors; log P_{calo} log P values calculated by molinspiration property calculator for the neutral species; log $P_{exp,}$ experimentally determined log P values by RP-HPLC.

These results suggest that there is little correlation between cytotoxicity and anti-proliferative activity for the 1,2,4-triazin-5-ones. If one compares the effect of R3 on the anti-proliferative activity against K-562 cells, an optimum exists for the pyrrolidine moiety. 4-Chloro substitution on the phenyl ring R2 not only raises the log P values, but lowers the effect on K- 562. Interestingly the existence of the chlorine atom in 3b and 3d seems to raise the growth inhibiting effect on HUVEC cells. An introduction of a morpholine group leads to a distinct decrease of any activity. Considering the estimated new cases (44,790 men and woman) and deaths (21,870 men and woman) from leukemia in the United States in 2009 [27] and the proceeding emergence of resistances against chemotherapeutic agents (multi-drug resistance), there is a demand for novel, more effective anti-cancer agents. Taking 1,2,4-triazin-5-one as lead structure for the development of less toxic and selective anti-leukemia drugs, further chemical modifications in the substitution patterns of the aromatic groups are envisioned for optimization of pharmacological activity. An introduction of hydrogen donor groups may be considered as well.

Melting points were determined on a Boetius hot-stage apparatus. Elemental analyses were performed by Leco Microlab, Inc., and determined values are within 0.4% of theory. NMR spectra were recorded on a Gemini 2000 operating at 399.96 MHz for 1HNMR and at 100.6 MHz for ^{13}C NMR spectra in DMSO-d6 which was also used as internal standard. Chemical shifts are given in 'd' units and refer to the center of the signal. EI-mass spectra were obtained

with an AMD402 mass spectrometer (AMD Intectra) at 70 eV. Reactions were monitored by TLC (Silica gel 60 F254, Merck) using chloroform/ether (7:3, v/v) and heptane/ ethylacetate (3:1, v/v) and compounds were detected with ultraviolet light (254 nm). Compounds 1a, 2a, 2b, 2e, 2g,17 1b,16 and 3e18 were obtained by published procedures[24].

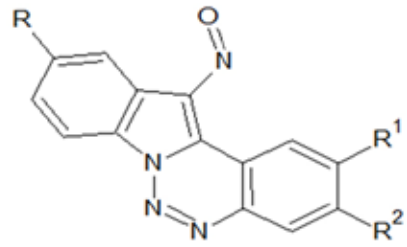
The development of new antibiotic resistant drugs has not been fulfilled yet and this question is accepted on priority universally. Recently, Albericio *et al.,* [25] have designed and synthesized a new class of pyrazole-containing 1,3,5-triazine derivatives and evaluated therein *in vitro* anti-microbial activity against a panel of bacterial and fungal strains using modified Kirby-Bauer disk diffusion method [26]. Compound 13 exhibited promising anti-bacterial activity against Gram-negative (*P. aeruginosa*, Zone of Inhibition (ZoI): 19 mm) and Gram positive (*M. luteus*, ZoI: 22 mm) bacterial strains. The SAR revealed that the presence of piperidine with benzylamine on the triazine ring proves to be a key factor for enhancing the anti-bacterial activity against *P. aeruginosa* and *M. luteus* bacterial strains. The combination of 1,3,5-triazine with pyrazole and piperidine rings was a promising scaffold for the development of new active anti-biotics in the near future. A set of novel 2,4,6 tri-substituted 1,3,5-triazines were synthesized and tested for *in vitro* antimicrobial activity by Mane and co-workers [27].



13

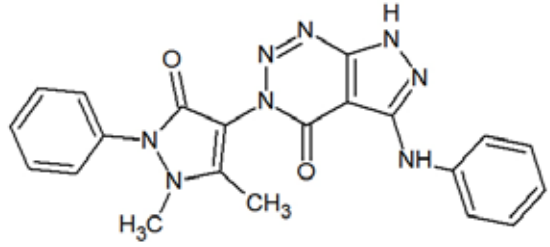
Girolamo Cirrincione *et al*. [28] synthesized some indolo [1,2-c]benzo[1,2,3]triazine analogs. Synthesized compounds were evaluated for *in vitro* anti-tumor activity against a panel of leukemia-, lymphoma-, carcinoma and neuroblastoma derived cell lines. Some of the synthesized compounds inhibited the proliferation of T and B cell lines at sub-micromolar concentrations and their activity against solid tumor cell lines was in the micromolar range. Indolobenzotriazine analog 14 showed most potent anti-tumor activity with IC_{50} in range of 0.08-0.7 µM. This compound was fully inhibitory to all the resistant cell lines thus suggesting that it neither is subject to the pump mediating the efflux of many antitumor drugs nor interferes with the DNA synthesis. The compounds (14) (IC_{50} range = 0.3-2.7 µM) and 15 (IC_{50} range = 1.9-9.5µM) displayed lower anti-proliferative activity against cell lines derived from solid tumors than that of Doxorubicin. All the synthesized compounds were also screened for antimicrobial activity.

All indolobenzotriazines were proved to be fairly potent and selective inhibitors of streptococcus and staphylococcus. Compounds (16) and (17) showed most potent antifungal activity. Compounds (18), (19), and (20) displayed most potent anti-bacterial activity. SAR studies revealed that maximum *in vitro* anti-tumor activity correlates with the presence of either a chlorine atom at position 10 (14) or a methyl group at position 2 (15). Furthermore, the absence of substituents at positions 10, and 2 (16), or the substitution of a chlorine atom for a methoxy (19) or nitro (20) group at position 10 or the substitution of a methyl group for a chlorine atom (18) at position 2 significantly decreased the activity.Moving the chlorine atom from position 2 to 3 (17) partially restores the anti-tumor activity *in vitro*. Maximum potency of anti-fungal activity correlates with the absence of substituents (16) or the presence of a chlorine atom at position 3 (17). Compound(17) was found to be the only compound capable of potently inhibiting the proliferation of both animal and fungal cells, whereas the derivatives endowed with the highest *in vitro* anti-tumor activity (14-15) were totally ineffective on the fungal growth. The potent and selective anti-bacterial activity is correlated with the presence of a chlorine atom at position 2 (18) or with a methoxy (19) or nitro (20) group at position 10.



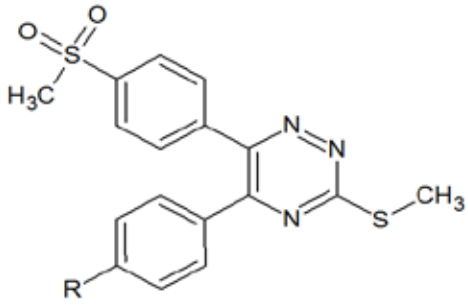
14 R=Cl, R_1=R_2=H, (IC_{50} Range= 0.08-0.7μM);
15 R=R_2=H, R1=CH_3, (IC_{50} Range = 1.9-9.5 μM);
16 R=R_1=R_2=H;
17 R=R_1=H, R_2=Cl;
18 R=R_2=H, R_1=Cl;
19 R=OCH_3, R_1=R_2=H;
20 R=NO_2, R_1=R_2=H

Samir Bondock *et al.* [29] synthesized a series of pyrazolo[3,4-d]triazine and screened them for *in vitro* anti-microbial activity against *Bacillus thuringiensis*, *Klebsiella pneumonia*, *Botrytis fabae* and *Fusarium oxysporum* by the agar diffusion method. Compound (21) exhibited significant anti-fungal activity. It was concluded that incorporation of anti-pyrine to the coumarin nucleus at position 3, via a carboxamide linker produces a high antimicrobial activity.



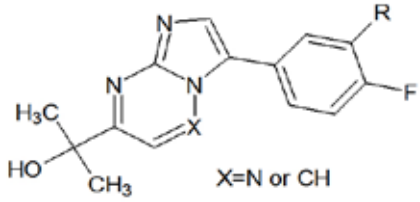
21

H. Irannejad *et al*. [30] reported that a series of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine derivatives were synthesized and their COX-1/COX-2 inhibitory activity as well as *in vivo* anti-inflammatory and analgesic effects were evaluated. All of compounds showed strong inhibition of COX-2 with IC_{50} values in the range of 0.1– 0.2 μM and in most cases had stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among them, 5-(4-chlorophenyl)-6-(4-(methyl sulfonyl) phenyl)-3-(methyl thio)-1,2,4-triazine was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib (SI = 405). Evaluation of anti-inflammatory and analgesic effects showed its higher potency than indomethacin and hence, could be considered as a promising lead candidate for further drug development. Furthermore, the affinity data of these compounds were rationalized through enzyme docking simulation and 3D-QSAR study by k-Nearest Neighbour Molecular Field Analysis (22).



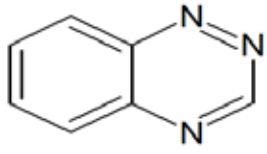
22

S. R. Jennings *et al.* [31] reported the Imidazo[1,2-b][1,2,4] triazines as a2/a3 subtype selective GABAA agonists for the treatment of anxiety

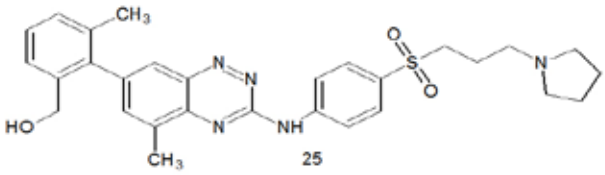


23

The prominent heterocyclic substrate which is present in numerous pharmacologically active molecules is 1,2,4-benzotriazine nucleus fused to a benzene ring.Many 1,2,4-benzotriazine possessing a wide spectrum of pharmacological activities (24).



The preclinical study of 3-amino-1,2,4-benzotrizine analogous to 25 and 26 have shown anti-tumor activity against sarcoma[32] due to their activities as inhibitors of Src kinases, and they may be effective as anti-neoplastic agents against pancreatic and breast, and stomach cancer cell lines.



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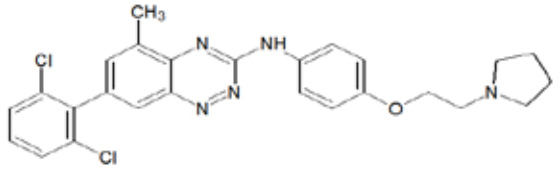
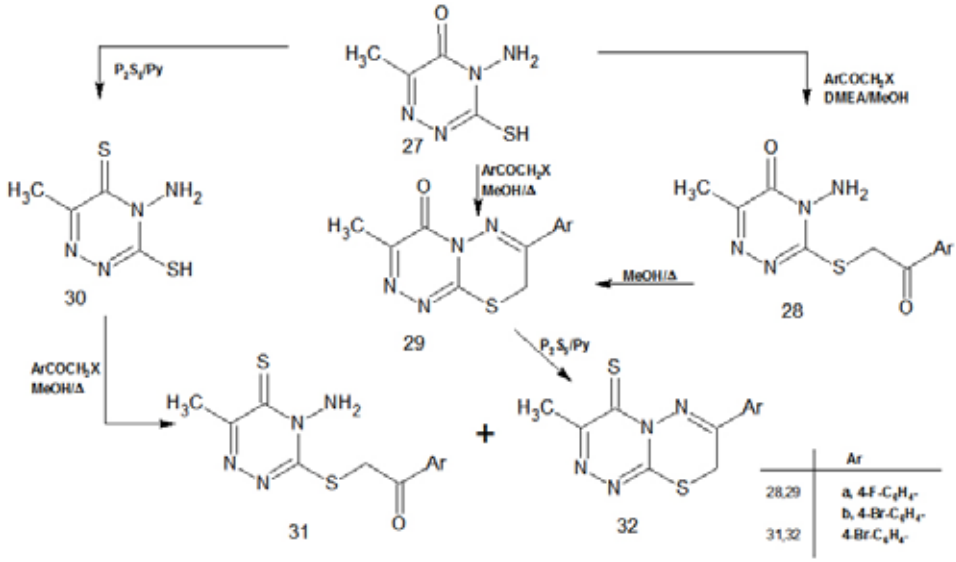


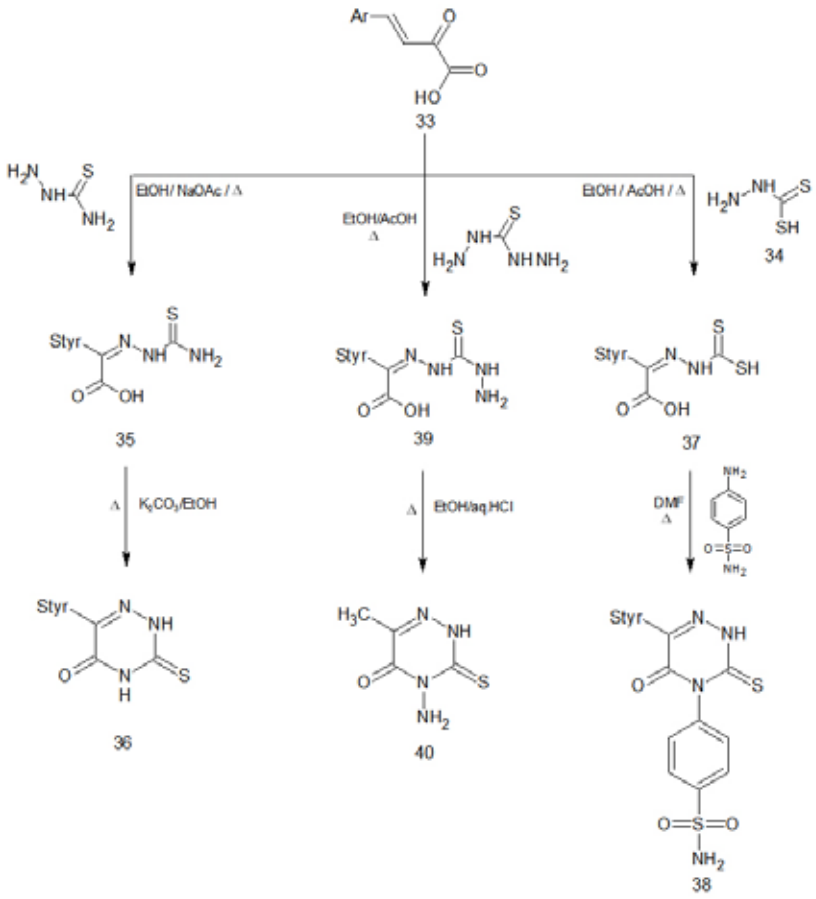
26

The anti-tumor activity, the SAR and whatever described the possible mode of action of 1,2,4-triazine derivatives, their N-Oxides, N,N-dioxides as well as the benzo- and hetero-fused systems are also being reported[33]. 3-Sulfanilamido5-dimethylethyl-1,2,4-triazine is manufactured and used as sulfa drug[34]. The 5-thioxo derivatives and 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one were allowed to react with phenacyl halides by giving different conditions of reaction to synthesize the derivatives of S-phenacyl derivatives [35] (Scheme 5).



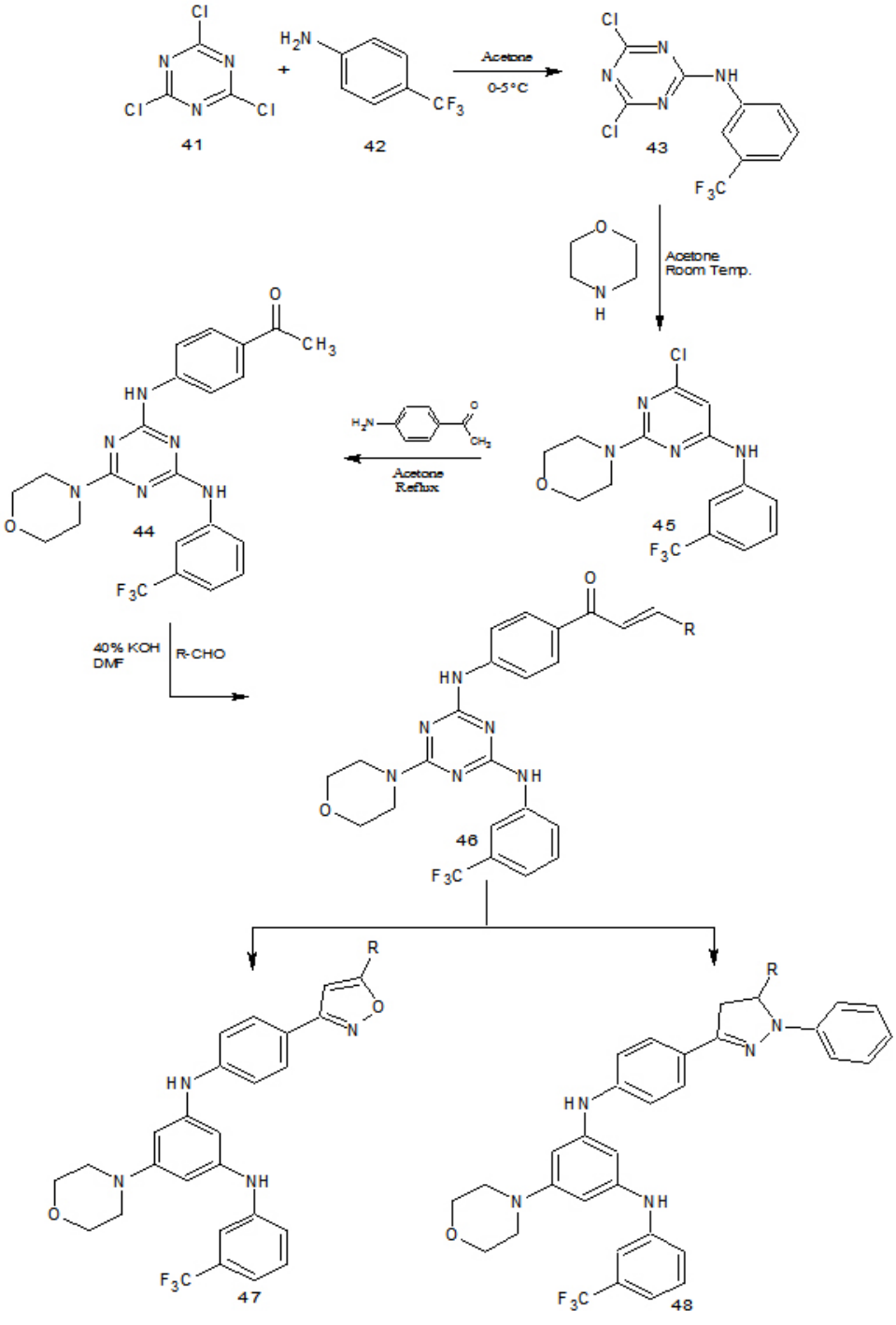
SCHEME 5

Reda *et al.* [36] have synthesized an affordable derivative of 1,2,4-triazin by the condensation reaction of 3-thioxo-1,2,4-triazine-5-one. A simple condensation afforded some new 3-thioxo-1,2,4-triazin-5-one derivatives (36, 38 and 40). Utilizing a facile condensation of (E)-4-(4'-bromo styryl)-2-oxo-3-buteneoic acid with thiosemicarbazide, dithioic formic acid hydrazide, and thiocarbahydrazide in different conditions. Structures of these compounds were confirmed by elemental and spectral analysis. The preliminary biocidal activity of these products were evaluated against some microbial and compared to Mycostatine and piperacillin as anti-biotics were most of the derivatives exhibiting good activity.



SCHEME 6

S-Triazine based chalcones results in the formation of derivatives of heterocyclic compounds like phenyl pyrazolines as well as isoxaxoles (Scheme 7), and then the structure of newly synthesized compounds were analyzed by elemental analysis and spectroscopic techniques like IR,^{1}H NMR,^{13}C NMR. The screening for antimicrobial activity have been done for the newly synthesized compounds against selected gram positive and gram negative like *S. aureus, S. pygenus, E. coli, P. aeruginosa* respectively and have also shown activity against fungal strains [37].


Cl
N
Cl
N
Cl
41
H_2N
+
CF_3
42
Acetone
0-5°C
NH
43
F_3C
O
N
H
Acetone
Room Temp.
45
44
CH_3
HN
NH
F_3C
Acetone
Reflux
40% KOH
DMF
R-CHO
R
46
47
48

SCHEME 7

CONCLUSION

It has been seen and identified from the literature survey and from the drugs used clinically that the biological potential of 1,2,4-triazine derivatives are very significant. The literature survey also revealed that 1,2,4-triazine derivatives have biological properties in diverse aspects. It has also been experienced that there are several easy synthetic routes to synthesize new chemo-therapeutic agents from 1,2,4-triazine derivatives.Importance of 1,2,4-triazine nucleus has attracted many researchers towards the heterocyclic chemistry.

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CYCLIC PEPTIDES AS THERAPEUTIC AGENTS AND BIOCHEMICAL TOOLS

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V.N. Rajasekharan Pillai**

ABSTRACT

There are many cyclic peptides with diverse biological activities, such as anti-bacterial activity, immune-suppressive activity, and anti-tumor activity, and so on. Encouraged by natural cyclic peptides with biological activity, efforts have been made to develop cyclic peptides with both genetic and synthetic methods. The genetic methods include phage display, intein-based cyclic peptides, and mRNA display. The synthetic methods involve individual synthesis, parallel synthesis, as well as split-and-pool synthesis. Recent development of cyclic peptide library based on split-and-pool synthesis allows on-bead screening, in-solution screening, and microarray screening of cyclic peptides for biological activity. Cyclic peptides will be useful as receptor agonist/antagonist, RNA=binding molecule, enzyme inhibitor and so on. New cyclic peptides will emerge as therapeutic agents and biochemical tools.

Keywords: Intein-based, Peptide, mRNA, microarray, split-and-pool.

INTRODUCTION

Cyclic peptides are polypeptide chains taking cyclic ring structure. The ring structure can be formed by linking one end of the peptide and the other with an amide bond, or other chemically stable bonds such as lactone, ether, thioether, disulfide, and so on[1-5]. N-to-C (or head-to-tail) cyclization is amide bond formation between amino and carboxyl termini, and many biologically active cyclic peptides are formed this way. Several cyclic peptides found in nature are used in clinic. The examples are gramicidin and tyrocidine with bactericidal activity, cyclosporin A with immune-suppressive activity, and vancomycin with anti-bacterial activity, and so on. While peptides have been generally considered to be poor drug molecules, there are some advantages of peptide drugs. The weakness of peptides and the strength will be discussed afterward. First, per oral absorption is poor for peptide drugs. In most cases, the route of administration is injection as peptides are not well absorbed in the gastrointestinal

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tract. Second, peptides are rapidly metabolized, even after successful absorption, by proteolytic enzymes[6-7]. Third, peptides usually do not cross cell membrane as some small molecules do. If the target of a peptide drug is in the cytoplasm, the peptide may not even reach the target. In spite of these limitations, peptides can be good alternatives to small synthetic molecules because of following advantages. Compared to small synthetic molecules, peptides possess less toxicity and they would not accumulate in organs. Even the fact that peptides get degraded rapidly can be a good thing.[8] Peptide drugs can be less harmful, after acting on target molecules, as they will disappear rapidly by proteolytic degradation. The degradation products are simply amino acids and would not have toxicity. Peptides can work on their targets very selectively, as the interaction with the targets is very specific compared to small molecules. Considering these strengths, it is not surprising that there are many peptide drugs available in the market.[52] These peptide drugs include receptor agonists and antagonists, peptide hormones and analogs, HIV protease inhibitors, and so on. In addition to the merits of peptides as drug molecules, cyclic peptides could make even better peptide drugs.[53]

Usually, cyclic peptides show better biological activity compared to their linear counterparts due to the conformational structures. The rigidity of cyclic peptides decreases the entropy term of the Gibbs free energy, therefore allowing the enhanced binding toward target molecules, or receptor selectivity. Another benefit from cyclic structure is the resistance to hydrolysis by exo-peptidases due to the lack of both amino and carboxyl termini. Cyclic peptides can be resistant even to endo-peptidases, as the structure is less flexible than linear peptides. Some cyclic peptides, though not all, can cross the cell membrane. Cyclosporin A is a good example of the membrane- permeable cyclic peptides. Until recently, it has been suggested that cyclic peptides cross the membrane better than the linear counterparts. To test this, a group of peptides have been synthesized, and their cell permeability was compared between cyclic and linear peptides. The results indicated that a peptide does not cross the membrane better simply because it is cyclized. If a certain cyclic peptide is membrane-permeable, it is because there are structural features allowing the molecule to cross the cell membrane. For example, cyclosporin A has several intra-molecular hydrogen bonds keeping hydrophilic groups from the surface of the molecule. Overall, structural rigidity, receptor selectivity, biochemical stability are general features of cyclic peptides and some cyclic peptides can be membrane permeable. These features allow cyclic peptides to be good therapeutic agents or biochemical tools, and efforts have been made to develop synthetic cyclic peptide with biological activity. In this review, the role of cyclic peptides in therapeutics and biochemistry will be described, as well as the approaches to develop cyclic peptide compounds for such purposes.[56]

THE ROLE OF CYCLIC PEPTIDES IN THERAPEUTIC

Bactericidal activity of Tyrocidine and Gramicidin S

Tyrocidine is a cyclodecapeptide with anti-bacterial activity. It was found from a culture extract of a soil bacillus, *Bacillus brevis*, as bactericidal agent as early as 1939 (Fig. 1 left top). Initially, this compound was characterized as a peptide lacking the free amino terminus, and therefore was proposed to have cyclic structure where amino terminus and carboxyl terminus are linked with an amide bond. While gramicidin S is a cyclic peptide, gramicidin refers to the mixture of linear pentadecapeptides with anti-bacterial activity. Tyrothricin, the mixture

of gramicidin and tyrocidine, was the first commercialized antibiotic and it is still used in clinic today. Gramicidin S, or Soviet gramicidin, is a cyclodecapeptide similar to tyrocidine, and was discovered in early 1940's for its anti-bacterial activity. Looking at the structure of these cyclic peptides, there can be two b-chains linked by proline residues and four intra-molecular hydrogen bonds. This model was proposed in 1950s and later confirmed by X-ray crystallography. As there are four intra-molecular hydrogen bonds, the peptide has a very rigid structure, a characteristic of cyclic peptides. In addition to the structural rigidity, these cyclic peptides are amphipathic. One side of molecule is hydrophobic while the other side is cationic. It appears that the cationic face interacts with lipid head groups of cell membrane which is negatively charged. This initial interaction is followed by interaction between hydrophobic portions of cyclic peptide and membrane lipid, resulting in the rupture of bacterial cell membrane[9-11]. The use of tyrocidine A is, however, limited to topical use as the membranolysis can happen even to the mammalian cells.

Cyclic Peptides Found in Natural Peptide Hormones

We can find several cyclic peptides from natural peptide hormones such as calcitonin, oxytocin, somatostatin, vasopressin, and so on. These peptides form rigid structure by forming disulfide bond connecting two Cysteine residues in the peptide[12-16].

APPROACHES TO DEVELOP CYCLIC PEPTIDE COMPOUNDS

As described above, there are many cyclic peptides used in clinic, and most of these originate from the natural cyclic peptides[17-18]. As several features make cyclic peptides attractive, lead compounds for drug development as well as nice tools for biochemical research, scientists made diverse efforts to develop biologically active cyclic peptide compounds. Peptides can be prepared by either genetic or synthetic method[19-21]. The genetic method, as described below, is usually limited to ribosomal 20 amino acids, whereas the sequence determination of hit compounds is straightforward[22-28]. The synthetic method can provide more versatile cyclic peptide compounds as the repertoire of amino acids and the way of forming cyclic peptides is diverse. Solid-phase peptide synthesis combined with split-and-pool synthesis can prepare fairly large libraries. However, sequence determination is challenging after screening of these libraries[29-30]. Conventional Edman degradation cannot be used for cyclic peptides once the free N-terminus disappears after cyclic peptide formation by N-to-C cyclization.[31-32] While tandem mass spectrometry (MS) can be used to analyze peptide sequences, the analysis of cyclic peptide sequence is more difficult than the analysis of linear peptide sequence. The fragmentation pattern is very complex for cyclic peptides. For a hypothetical cyclic peptide containing only 3 amino acids, namely cyclo (ABC), the fragments formed from tandem MS would be ABC, BCA, CAB, AB, BC, CA, A, B, and C (total 9), while the linear peptide ABC would yield ABC, AB, BC, A, B, and C only (total 6). The fragmentation pattern gets more complex as the number of amino acid increases. Therefore, sequence analysis of cyclic peptides by tandem MS is not practical where the quantity of peptide from each micro-bead of split-and-pool synthesis library can be as little as about 100 pmol for -90 mm beads[33].

In the following paragraphs, both genetic and synthetic approaches to develop cyclic peptide compounds will be discussed.

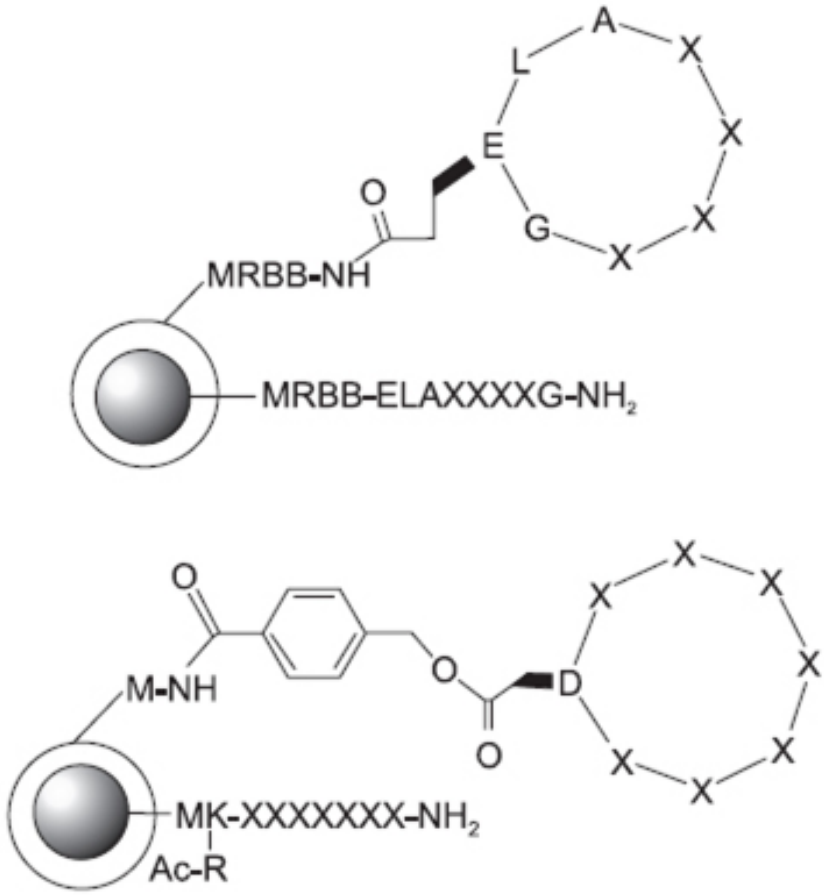


Fig 1: Structures of cyclic peptide libraries based on split-and-pool synthesis. Top: Cyclic peptide for on-bead screening. Bottom: Cyclic peptide for in-solution screening. Cyclic peptides can be released from the bead by hydrolysis of ester linkage, and then the remaining linear peptides are used for sequence determination.

THE CHEMICAL SYNTHESIS OF PEPTIDES

Peptides are the long molecular chains that make up proteins. Synthetic peptides are used either as drugs (as these are biologically active) or in the diagnosis of disease. Peptides are difficult to make as the synthetic chemist must ensure that the amino acids that make up the chain are added in the correct order and that they don't undergo any other reactions. This involves adding one amino acid, washing away any unreacted acid then adding the next and so on.[34-37] As can be imagined, this is very time consuming and only gives very low yields.

A technique that has been relatively recently developed involves attaching one end of the peptide to a solid polymer, meaning that the peptide cannot get washed away alongwith the excess acid. This is much quicker than classical synthesis, and leads to dramatically improved yields. The process consists of five steps carried out in a cyclic fashion[38].

Step 1 : Attaching an amino acid to the polymer

The amino acid is reacted with a molecule known as a "linkage agent" that enables it to attach to a solid polymer, and the other end of the linkage agent is reacted with the polymer support.[40]

Step 2: Protection

An amino acid is an acid with a basic group at one end and an acid group at the other. To prevent an amino acid from reacting with itself, one of these groups is reacted with something else to make it unreactive.

Step 3: Coupling

The protected amino acid is then reacted with the amino acid attached to the polymer to begin building the peptide chain.

Step 4 :Deprotection

The protection group is now removed from the acid at the end of the chain so it can react with the next acid to be added on. The new acid is then protected (**Step 2**) and the cycle continues until a chain of the required length has been synthesised.

Step 5: Polymer removal

Once the desired peptide has been made, the bond between the first amino acid and the linkage agent is broken to give the free peptide.

A peptide is a chain of special acids called amino acids linked together by bonds known as amide bonds. A protein consists of one peptide folded in a particular way, or several peptides folded together. Such peptides are synthesised very rapidly within living cells, but until recently could only be artificially synthesised in very long, slow processes that had poor yields and gave impure products. Recently a new technique known as solid phase peptide synthesis (SPPS) has been developed. SPPS results in high yields of pure products and works more quickly than classical synthesis, although still much more slowly than among living cells.

USES OF SYNTHETIC PEPTIDES:

Synthetic peptides have two main uses: as peptide drugs and as peptides for diagnostic purposes.

Peptide drugs

Peptide drugs are either naturally-occurring peptides or altered natural peptides. There are many naturally-occurring peptides that are biologically active. If a patient does not naturally produce a peptide that they need, this peptide can be synthesised and given to them. In addition, the amino acids in an active peptide can be altered to make *analogues* of the original peptide. If the analogue is more biochemically active than the original peptide it is known as an *agonist* and if it has the reverse effect is known as an *antagonist.*[41-44] Contraceptives have been made by synthesising the antagonists of fertility peptides.

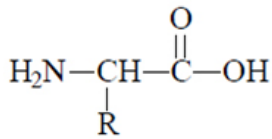
Diagnostic peptides

Peptides can be designed that change colour under certain conditions, and these can be used for diagnostic purposes. For example, a chromogenic peptide substrate can readily detect the presence, absence and varying blood levels of enzymes that control blood pressure and blood clotting ability.

Since 1973, the SPPS laboratory at Massey University has supplied peptides for research purposes to universities, CRIs, research institutes and private industry. These peptides have been used for medical research into areas such as heart disease, leprosy and tuberculosis. The laboratory itself is involved in research into and development of synthetic methods and peptide production[45].

INTRODUCTION TO PROTEIN CHEMISTRY

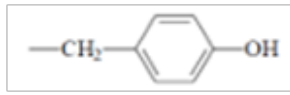
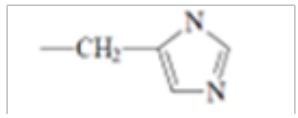
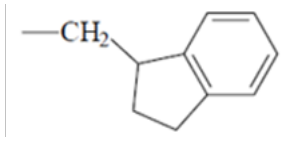
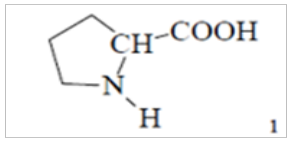
Peptides are polymers of amino acids made using anything from two to hundreds of amino acids. They are all based on the α-amino acid structure



There are twenty amino acids that commonly occur in nature (**Table 1**) and many others have been synthesized.

Table 1: Side chains of the Common Naturally Occurring Amino Acids

Name	Side chain	Protection
Glycine	-H	Never necessary
Alanine (ala)	$-CH_3$	Never necessary
Valine (val)	$-CH(CH_3)_2$	Never necessary
Leucine (Leu)	$-CH_2-CH(CH_3)_2$	Never necessary
Isoleucine(ile)	$-CH(CH_3)-CH_2-CH_3$	Never necessary
Lysine (lys)	$-CH_2-CH_2-CH_2-CH_2-NH_2$	Protecting group is tBOC
Arginine (arg)	$CH_2-CH_2-CH_2-NHC(NH_2)(NH)$	Protecting group is PMC
Aspartic acid (asp)	$-CH_2-COOH$	Protecting group is tBu
Asparagine (asn)	$-CH_2-CONH_2$	Protecting group is tBu
Glutamic acid (glu)	$-CH_2-CH_2-COOH$	Protecting group is tBu
Glutamine (gln)	$-CH_2-CH_2-CONH_2$	Protecting group is Trt
Theronine (thr)	$-CH(OH)(CH_3)$	Protecting group is tBu
Methionine (meth)	$-CH_2-CH_2-S-CH_3$	Protecting group is S=O
Cysteine (cys)	$-CH_2-SH$	Protecting group is Trt and tBu

Serine (ser)	-CH_2-OH	Protecting group is tBu
Phenylalanine (phy)	-CH2-C_6H_6	Never necessary
Tyrosine (tyr)		Protecting group is tBu
Histidine (his)		Protecting group is Trt
Tryptophan (trp)		Protecting group is tBOC
Proline (pro)		Never necessary

These peptides (or combinations of them) fold in characteristic ways to give proteins. Among mammals, all optically active amino acids are in the L form, so one change that can be made to peptides is to substitute a D amino acid for one of the amino acids in the chain.

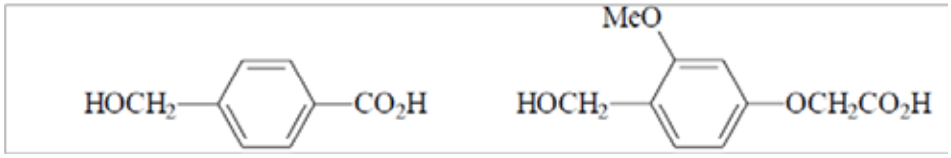
SOLID PHASE PEPTIDE SYNTHESIS

Peptide synthesis is much more complicated than simply forming amide bonds by mixing the desired amino acids together in a test tube.[47-48] With twenty natural amino acids and a number of unnatural ones as well the possible combinations formed with this technique are numerous. This complexity makes the synthesis of peptides both fascinating and challenging.

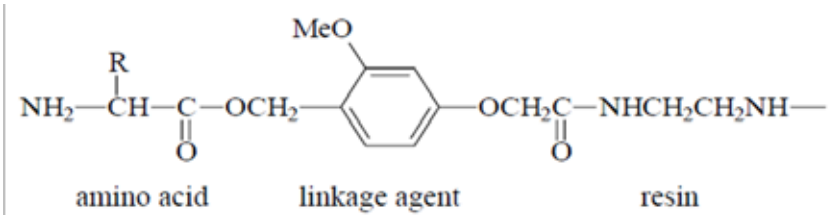
If solutions containing two amino acids are mixed together, four different dipeptides (as well as other longer peptides) will be formed. For example, for a mixture of glycine and alanine the four dipeptides would be glygly, glyala, alagly, alaala.[49-50] In this representation of peptides, the free amino group or N-terminus is on the left hand amino acid and the free carboxylic acid group, the C-terminus is at the right hand end. To ensure that only the desired dipeptide is formed, the basic group of one amino acid and the acidic group of the other must both be made unable to react. This 'deactivation' is known as the *protection* of reactive groups, and a group that is unable to react is spoken of as a protected group.[51-52] In classical organic synthesis, the acids are protected, allowed to react and deprotected, then one end of the dipeptide is protected and reacted with a new protected acid and so on. In SPPS, the amino acid that will be at one end of the peptide is attached to a water-insoluble polymer and remains protected throughout the formation of the peptide, meaning both that fewer protection/ deprotection steps are necessary and that the reagents can easily be rinsed away without losing any of the peptide.[53-55]

Step 1: Attaching an amino acid to the polymer

Peptide chains have two ends, known respectively as the N-terminus and the C-terminus, and what end is attached to the polymer depends on the polymer used. This article assumes that polyamide beads are used wherein the C-terminus of the peptide is attached to the polymer. The attachment is done by reacting the amino acid with a linkage agent and then reacting the other end of the linkage agent with the polymer. This means that a peptide polyamide link can be formed that will not be hydrolysed during the subsequent peptide-forming reactions. Common linkage agents are di- and tri-substituted benzenes such as those shown below:

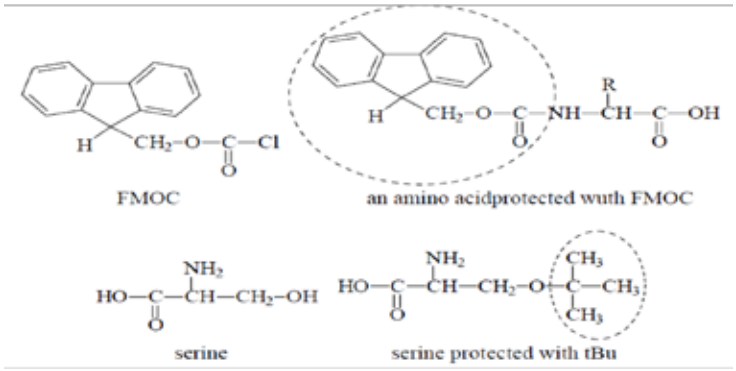


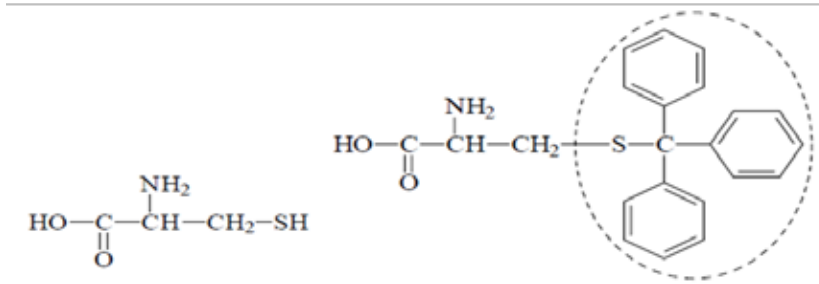
These then join the C-terminus amino acid and resin together as follows:

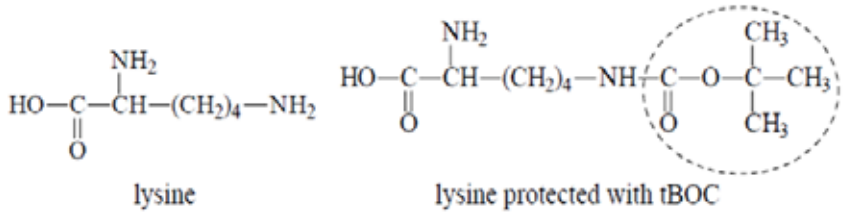


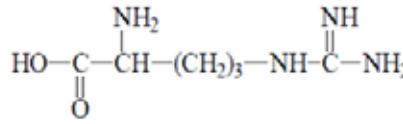
Step 2: Protection

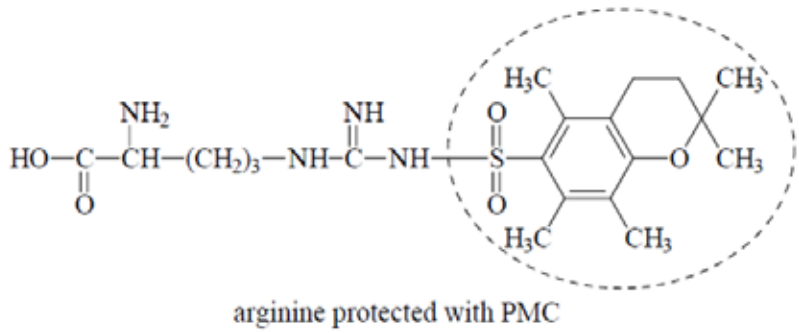
Amino acid also needs to have its amino group protected to prevent the acids reacting with each other. This is done by protecting it with FMOC (9-fluorenylmethoxy-carbonyl). In addition, any amino acid side chains that are aromatic acid, basic or highly polar are likely to be reactive (see **Table 1**). These must also be protected to prevent unwanted branched chains from forming. There are four main groups used in this way: tBu (a tertiary butyl group), Trt (a triphenylmethyl group), tBOC (a tertiary butyloxycarbonyl group) and PMC (a 2, 2, 5, 7, 8-pentamethylchroman-6-sufonyl group). Examples of a carboxyl group protected with FMOC and examples of the different types of side chain protection are given below.









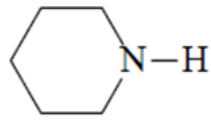


Step 3 : Coupling

The FMOC protected amino acid is then reacted with the last amino acid attached to the polyamide. The reaction is catalysed by DCC (1, 3 dicyclohexylcarbodiimide), which is itself reduced to DCU (1,3-dicyclohexylurea).

Step 4 : Deprotection

Excess DCC is washed off the insoluble polymer with water, then the FMOC group removed with piperidine (a cyclic secondary amine). This is a trans-amidification reaction.

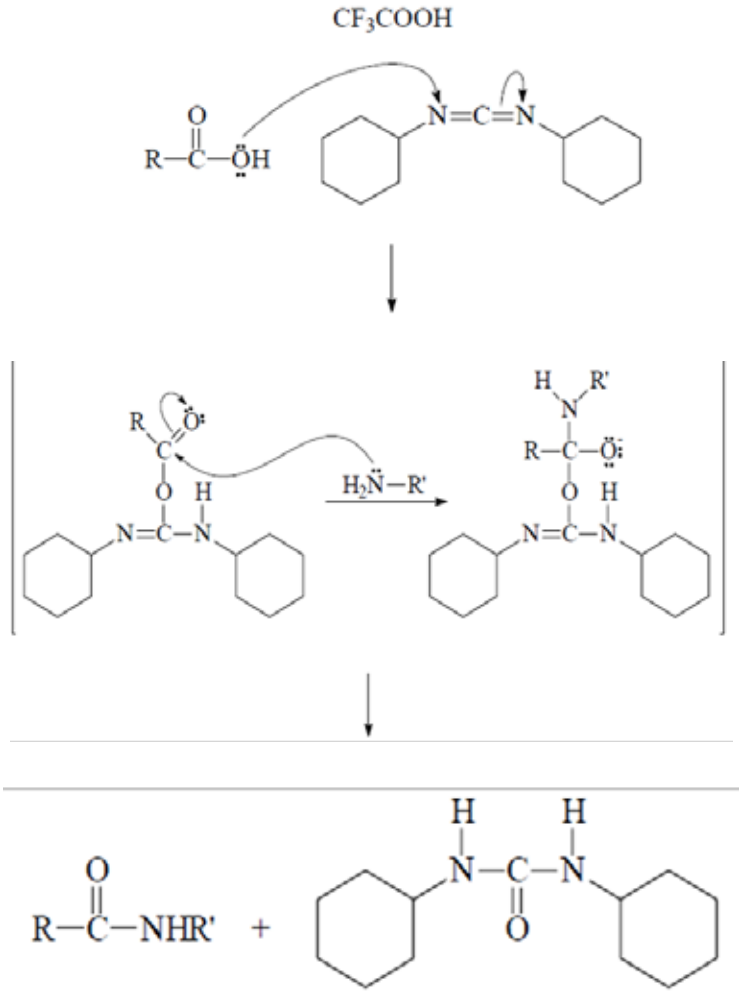


piperidine

Steps 2 to **4** are repeated as each new amino acid is added onto the chain until the desired peptide has been formed.

Step 5 : Polymer Removal

Once the peptide is complete, it must be removed from the polyamide. This is done by cleaving the polyamide - peptide bond with a 95% solution of trifluoro acetic acid (TFA). The side-chain protecting groups are also removed at this stage.



Reaction scheme of amide bond formation

PRACTICAL AND FINANCIAL ADVANTAGES OF SPPS

The primary advantage of SPPS is its high yield. As peptides consist of several amino acids, if the yield for each amino acid addition is much less than 100%, overall peptide yields are negligible. For example, if each amino acid addition has a 90% yield then the overall yield of a 50 amino acid peptide is only 0.5%. Modern SPPS instrumentation pushes coupling and deprotection yields to greater than 99.99%, giving an overall yield of greater than 99% for a 50 amino acid peptide.

SPPS is also much quicker than conventional step-by-step solution synthesis. With SPPS, a 20 amino acid peptide can be synthesized in a 24-hour period and longer ones in less than a week. With the advent of automated synthesizers and sophisticated analytical and purification equipment the peptide chemist can now make peptides in the range of 20-50 amino acids in length and in amounts from 20-100 milligrams. This is often more than enough for biochemists and biologists to carry out extensive pilot studies and as they often only look at a particular peptide once this speed is particularly useful. If very large amounts of peptide are required (e.g. for the industrial production of peptide drugs) ,then this speed is sacrificed for purity. However, production rates are still high, and hundreds of grams of peptide can be produced on kilograms of polymer every year. As an often-only milligram of polymer is needed per dose, this represents hundreds of thousands of doses.[57]

ENVIRONMENTAL IMPLICATIONS

SPPS, like much of organic chemistry, makes use of organic solvents which are hazardous to the environment. The SPPS group at Massey University is currently researching ways of producing peptides in aqueous or partially aqueous (e.g. water/ethanol mixtures) solutions to avoid the use of organic solvents. The cyclotides are a family of plant-derived proteins that occur in plants from the *Violaceae(violet), Rubiaceae (coffee)* and *Cucurbitaceae (cucurbit*) families and have a diverse range of biological activities, including uterotonic, anti-HIV, anti-microbial, and insecticidal activities; the latter suggests their natural function lies in plant defence. Individual plants express suites of 10–100 cyclotides. Cyclotides comprise w30 amino acids, contain a head-to-tail cyclised backbone, and incorporate three disulfide bonds arranged in a cystine knot topology. The combination of a knotted and strongly braced structure with a circular backbone renders the cyclotides impervious to enzymatic breakdown and makes them exceptionally stable. The cyclotides are the largest of several groups of naturally occurring circular proteins that have been discovered in bacteria, plants and animals over recent years.[58] Next section describes the discovery of the cyclotides in plants, their structural characterisation, evolutionary relationships and their applications in drug design.[59-60]

Cyclotides: Structures and Activities

Cyclotides are small disulfide-rich proteins found in plants of the Rubiaceae, Violaceae and Cucurbitaceae families, with recent studies suggesting that they might also be found in other families. Individual plants express suites of 10–100 cyclotides, distributed in a wide range of tissues, including leaves, stems, flowers and roots, as highlighted for a selection of

cyclotides. A full list of cyclotide sequences is available on Cybase. They were originally discovered in indigenous medicinal applications, where women in Africa used a tea made from the Rubiaceae plant *Oldenlandia affinis* to accelerate childbirth. Gran subsequently discovered that the active uterotonic agent was a peptide of around 30 amino acids, which was named kalata B1.[67] Many years later, it was established that it was a head-to-tail macrocyclic peptide, which contained a cystine knot motif. Subsequently, a large number of similar macrocyclic peptides from plants have been discovered and these are now known as the cyclotides, the term being defined in our 1999 paper in the *Journal of Molecular Biology*. Kalata B1 has now been discovered in five plant species, but in general different plants express different suites of cyclotides. Cyclotides are distinguished from many other proteins in that they are exceptionally stable. In particular, they are highly resistant to proteases, are thermally stable, and are resistant to chemical chaotropic. All of the early studies on the structural characterization of cyclotides involved NMR spectroscopy as the primary characterisation technique shows the consensus NMR structure of cyclotides and highlights a number of important features, including the cystine knot, a small b-sheet structure and a series of loops and turns that project from the molecular core. Recently, we reported the crystal structure of a cyclotide and these structural features were verified using this technique. Fig.1 also highlights the combinatorial nature of cyclotides, which tolerate a wide range of sequence substitutions at all non-Cys positions, apart from a few conserved residues in their backbone, notably,a highly conserved Glu residue in loop 1 and an Asn or Aspresidue in loop 6.

Cyclotides have a range of biological activities, including uterotonic activity, anti-HIV activity, neurotensin antagonism, haemolytic activity, anti-microbial activity, cytotoxic activity, insecticidal activity and anthelmintic activity. Only three of these activities that are of greater relevance to toxicology are discussed here, namely haemolytic, anti-HIV and insecticidal activities. First, haemolytic activity was one of the original activities discovered for the cyclotide Viola peptide 1. Numerous cyclotides have since been tested for this activity and typically most have mild potency, with HD50 values>10 mM; none are as potent as melittin, from bee venom, the gold standard for haemolytic activity of a peptide. Haemolysis is a toxic activity that might well be important for cyclotides as host defence peptides but this specific role has not yet been investigated. Interestingly, synthetic analogues of cyclotides in which the backbone is broken are essentially devoid of haemolytic activity. This trend of activity being lost upon the backbone being rendered acyclic is common not only to haemolytic activity but also to anti-HIV activity of cyclotides. The second activity of cyclotides, i.e., anti-HIV activity, has been reviewed extensively. Typically, cyclotides are effective against virus infected cells with EC50 values of approximately 100 nM and it was this activity, identified in early screening studies, which attracted interest in cyclotides.[61]However, cyclotides are not currently being pursued clinically as anti-HIV agents because their therapeutic index (i.e., the ratio of their therapeutic to toxic effects) is too narrow. Some examples of the anti-HIV activity of cyclotides also emphasises that synthetic linear examples are inactive, confirming the important role of the cyclic backbone in activity.

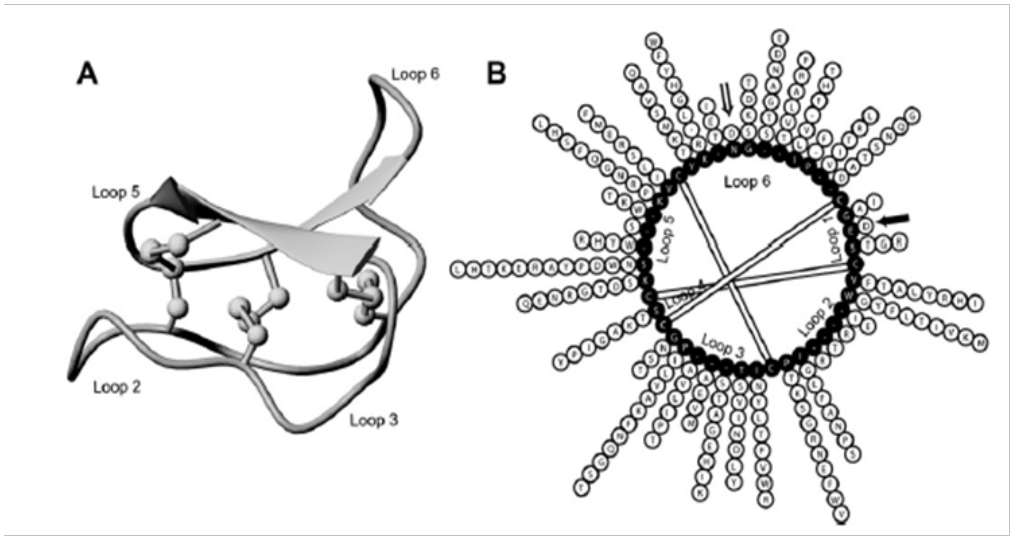


Fig2: Cyclotide structures and sequences. Panel A shows the prototypic cyclotide kalata B1 (PDB ID:1NB1), illustrating the cyclic backbone and cystine knot motif, along with a small b-sheet and loops between successive Cys residues. Panel B shows a diversity wheel representation of sequence variation seen in cyclotides. The inner circle shows the consensus sequence of all cyclotides, with the radiating arms showing residues that are substituted at corresponding positions in currently known cyclotides. At each position amino acids are sorted according to their frequency, the closer to the wheel being the more conserved. There are only a few positions, apart from the completely conserved cystine residues, that are almost invariant. Key positions include an Asn or Asp residue in loop 6 (light arrow) and a Glu, or rarely Asp (dark arrow) in loop 3.

CONCLUSION

Cyclic peptides are naturally occurring mini- protein bioactive molecules with interesting pharmacological and biochemical properties. They are present in several species of plant families such as *Annonaceae, Araliaceae, Asteraceae, Caryophyllaceae, Euphorbiaceae, Fabaceae, Labiatae, Linaceae, Olacaceae, Rhamnaceae, Rubiaceae, Rutaceae, Schizandraceae, Solanaceae*, and *Violaceae*, Basidiomycetes is the group of higher fungi and these cyclopeptides display various biological properties such as protease inhibitory, anti-microbial, insecticidal, cytotoxic, anti-human immune-deficiency virus, cytotoxic, anti-malarial, estrogenic, sedative, nematicidal, immune-suppressive, and enzyme-inhibitory activities. Gramicidin S is an example of naturally occurring cyclic decapeptide extracted from the soil bacterium *Aneurini bacillus*.The biological characteristic features of cyclic peptides are different from linear peptides. There are different ways to cyclize peptides. The linear peptide strand can be cyclized not only from head to tail, connecting the C and N-termini, but also by linking to amine and carboxylic functions in amino acid side chains, giving side-chain-to-head or side-chain-to-tail connections. Side-chain-to-side-chain bridges have also been observed.

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HYPOXIC MECHANISMS IN THE CARBON MONOXIDE -INDUCED INJURY TO CARDIAC & OTHER TISSUES IN ACUTE POISONING : A NOTE ON THE ROLE

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ABSTRACT

In this paper, the role played by hypoxic mechanisms in Carbon Monoxide (CO) induced injury to cardiac and other tissues in acute poisoning has been discussed. Acute poisoning is mainly due to tissue hypoxia. Signs and symptoms of acute CO poisoning can be present at Carboxyhaemoglobin (COHb) levels ranging between 3 to 24%. Exposures resulting in COHb levels greater than 50% are frequently fatal. Formation of COHb is the principal hypoxic mechanism that decreases oxygen carrying capacity of the blood and also impairs the release of oxygen from Hb for its utilization in tissues. Through hypoxic mechanisms, CO may affect any tissue, particularly tissues with high oxygen utilization requirements like brain, liver, kidney and heart.

Keywords: Carbon Monoxide, Hypoxic mechanisms, Poisoning, Carboxyhaemoglobin, Toxicity.

INTRODUCTION

The toxic gas, Carbon Monoxide (CO), which is colorless and odorless, is produced as a byproduct of incomplete combustion of carbon-based fuels and substances. Human beings are exposed to carbon monoxide usually through inhalation. Information on its absorption or toxicity resulting from oral or dermal exposures is not known to common public. Carbon monoxide affects cell metabolism through both hypoxic and non-hypoxic mechanisms. The effects produced by both mechanisms, are largely due to the ability of carbon monoxide to bind to heme and alter the metabolism and/or function of heme proteins.

Carbon monoxide exposure at levels producing hypoxia through hypoxic mechanisms is expected to affect any tissue, particularly tissues with high oxygen (O_2) utilization requirements

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like heart, liver, kidney, and brain. The brain and the heart, are the organs most susceptible to CO toxicity, because of their high metabolic rates. The degree of injury directly associates with the duration and the severity of the exposure. Formation of Carboxyhemoglobin (COHb) is the principal hypoxic mechanism. This formation decreases the O_2 carrying capacity of the blood and also impairs the release of O_2 from Hb for its utilization in tissues. Carbon monoxide decreases O_2 storage in muscle cells through similar mechanisms by binding to myoglobin and displacing O_2 from it. Blood COHb levels have not been shown to be a reliable predictor of severity of acute toxicity, although binding of carbon monoxide to Hb is the primary component of the hypoxic mode of action of carbon monoxide. This can be due to the time elapsed between the removal of the subject from exposure to CO to COHb measurement; and can also be due to the effects of emergency medical treatment with oxygen.

Acute carbon monoxide poisoning is mainly due to tissue hypoxia. In general, signs and symptoms of acute carbon monoxide poisoning can be present at COHb levels ranging from 3 to 24%. [1] More severe signs of carbon monoxide poisoning are poorly correlated with blood COHb levels, with loss of consciousness occurring at a mean level of 24.3% (range: 2–70%);and fatality at a mean level of 32.1% (range: 3.0–60%)[1]. Exposures resulting in COHb levels >50% are frequently fatal.[2] Persistent neurologic sequelae, delayed in onset, can also occur. Although severe carbon monoxide toxicity primarily derive from hypoxia, the relationship between blood COHb levels and signs indicative of life-threatening toxicity is highly uncertain (eg., convulsions, coma, and cardiopulmonary depression).

In subjects with compromised cardiovascular function (e.g., coronary artery disease), adverse cardiovascular effects are associated with the carbon monoxide exposures that result in blood COHb levels ≥2.4%, with effects occurring at the lowest levels. And blood COHb levels between 2.4 and 5.9% exacerbates the underlying cardiovascular disease, including enhancing myocardial ischemia and increasing cardiac arrhythmias. Continuous exposure of healthy subjects, to carbon monoxide resulting in blood COHb levels of 2.4 and 5.1% produced many P-wave deviations under resting conditions.[3] Under conditions of cardiac ischemia, tissue hypoxia secondary to the elevated COHb levels is thought to be a contributing factor to the cardiac effects in patients with coronary artery disease. However, direct cellular effects of carbon monoxide on cardiac muscle are also important. These include modulation of coronary arteriole calcium-activated potassium channels. They are inhibited under hypoxic/ischemic conditions.[4] CO also binds with myoglobin which is another heme protein. It has an affinity approximately 60 times greater than that of oxygen. This binding is enhanced under hypoxic conditions. This binding may partially explain the myocardial impairment that occurs with low-level exposures in patients with ischemic heart disease.[5]

High levels of carbon monoxide after acute exposure produce symptoms of central nervous system toxicity. Though mechanisms of acute and delayed adverse nervous system effects are not established conclusively, tissue hypoxia secondary to COHb formation may be a contributing factor, particularly in association with high levels of blood COHb (>60%)[3]. The hypoxic state also triggers release of nitric acid from platelets and endothelial cells, leading to the formation of the free radical peroxynitrate. This causes mitochondrial dysfunction with a marked decrease in cytochrome oxidase, capillary leakage and apoptotic cell death. Direct

cellular effects of carbon monoxide like ATP depletion, excitotoxicity, oxidative stress and postischemic reperfusion injury also contribute to neurotoxicity. Cerebrovascular vasodilation and increased cardiac output occur as compensatory mechanisms to maintain O_2 delivery to the brain, under conditions of hypoxia induced by COHb formation.[6]

Exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements. The kidney is the greatest contributor to basal metabolic rate next only to the brain because of the use of ATP-dependent active transport processes. Carbon monoxide-induced hypoxia decreases the availability of oxygen to produce ATP in renal mitochondria, which produces adverse effects to the kidneys. Acute renal failure secondary to rhabdomyolysis has been observed in cases of acute carbon monoxide poisoning.[7] Visual field deficits, retinal hemorrhage & optic atrophy have been associated with severe CO poisoning in humans. The fetus is particularly vulnerable to maternal carbon monoxide exposure. Carbon monoxide in the maternal system distributes to fetal tissues. Measurements of fetal COHb concentrations in fetal and maternal blood of nonsmoking women have found fetal COHb concentrations to be approximately 10–15% higher than maternal blood[8].

Hematological effects of carbon monoxide include compensatory responses to tissue hypoxia resulting from the binding of carbon monoxide to Hb. Because carbon monoxide has a much higher affinity for Hb than O_2, greater than 200 times that of O_2, with relatively low partial pressures of carbon monoxide, O_2 is displaced from Hb. Binding of carbon monoxide to Hb has two effects:(a) the amount of O_2 that can be stored on Hb for delivery to tissues, decreases; and (b) it impairs the release of O_2 from Hb for its diffusion into tissues. CO thus causes a leftward shift of the oxyhemoglobin dissociation curve.[5] At sufficient levels of COHb, the combined effect results in tissue hypoxia, the principal mechanism of many adverse effects of carbon monoxide exposure. To maintain O_2 delivery to tissues under conditions of hypoxia, compensatory hematological responses like increased blood volume, erythrocyte count, hematocrit, and Hb occur.

Targets of carbon monoxide through non-hypoxic mechanisms include components of many physiological regulatory systems, such as brain and muscle oxygen storage and utilization (neuroglobin, myoglobin); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); nitric oxide cell signaling pathway (e.g., nitric oxide synthase); steroid and drug metabolism (cytochrome P450), energy metabolism and mitochondrial respiration (cytochrome c oxidase, NADPH oxidase); and Reactive Oxygen Species(ROS) (catalase, peroxidases); and various transcription factors. Most of these non-hypoxic mechanisms have been attributed to the binding of Carbon Monoxide to heme proteins other than Haemoglobin (Hb)[3].

The current understanding of principal mechanisms underlying the hypoxic mechanism of carbon monoxide is the higher affinity of carbon monoxide for Hb than O_2 and the increased binding affinity for O_2 from COHb. Binding of O_2 and carbon monoxide to the four heme moieties of Hb is actually cooperative.[9] With successive additions of carbon monoxide or O_2, the associative reaction rate becomes faster, impairing the release of O_2 from Hb for utilization in tissues.[10] Although the blood COHb level reflects the current carbon monoxide body burden, measurement of blood COHb has not been shown to be a reliable predictor of severity of acute

toxicity.[1] Cardiac enzyme markers are associated with elevated risk for long-term cardiac mortality following carbon monoxide poisoning; And the biochemical markers for brain injury, such as neuron-specific enolase and S-100 beta protein, have not been found to reliably correlate with severity of poisoning[11]. Although hypoxic mechanisms of action of carbon monoxide are well established (i.e., those related to formation of COHb), further research is needed in the area of biomarker profiles for carbon monoxide poisoning to optimally treat patients who were exposed to this toxic gas.

Conflict of Interest: None

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INCUBATION CENTRES: IMPACT ON RESEARCH AND ENTREPRENEURSHIP ASPIRANTS

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ABSTRACT

An Incubation leverages upon the youth to spur greater innovation led start-ups for generating more value to society and economy by creating globally competitive products and services. As a pilot project, 11 Incubation Centres were set up providing a platform for collaboration with agencies to have extensive gainful job opportunities and exciting career growth opportunities leading to a start-up culture in NCT Delhi. It helped in creating a culture of entrepreneurship, start-ups and Intellectual Property that can lead to value creation, jobs and employment and do social and economic good. The Delhi Government came up with a unique Incubation project for the students pursuing higher studies and aspiring with their brilliant ideas looking for a hand holding to explore their research work and establish themselves with their business set up. To accomplish the task, students were encouraged for startups, the mindset of faculty were changed and inculcated an aspiration of entrepreneurship among parents. The host institutions made all efforts recommending alliances for incubators with experts from technology, marketing, financing domains so that start-ups can be guided. Although, with the advance of time, only a few incubators could take off on a sustainable business model. Some fell short of the execution of basic idea, a few switched over to better opportunities, some of them wondered as to how to use the seed money, several of them were trapped in the nitty-gritty of setting up the company and paper work, quite a few dropped in between as they exhausted the funds beforehand and a number of them evaded with the seed money received. The project could not yield the desired result for want of expertise in the field, paper work and the mode of financial loans imparted. Overall, targeting the number of incubates became the criteria rather than developing a unique sustainable model of technology for many of the institutes. Despite these concerns, it is considered to be a good start and a platform for those scientific minds that would have otherwise missed the opportunity of innovation.

Keywords: Incubation centres, incubatees, incubators, start-ups.

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INTRODUCTION

World over Universities like Stanford, MIT, Harvard have a culture of student startups that go on to become leading global companies like Google, Facebook, Yahoo, and so on, whereas, most of the Indian Universities focus on academics and research, with a little success on startups, and thus a gap was inevitable.

Delhi Government in its endeavor to enhance the quality of research, in the financial year 2015-16, earmarked over Rs 20 crore for the setting up of six Incubation Centres in Delhi, and a seed money of Rs 1.5 crore was allocated to each of the Centre. In the second phase, 2016-17, same amount was granted for establishing five more Incubation Centres. The Incubation Centres were expected to bridge the gap between academic and real-life practice by transforming ideas and concepts into reality. Experience gained at such a Centre was expected to be a motivational force for those aspiring to work and find suitable career opportunities in unexplored and challenging areas, besides encouraging Entrepreneurship and Innovation.

Proposals were sought from the interested educational institutes functioning under the Directorate of Higher Education and Directorate of Training and Technical Education (DTTE) to set up Incubation Centres. Based on the interest and magnitude of research work, the institutes were selected. These selected institutes were asked to form a society and register under the Societies Registration Act and a committee of experts was to look into the day to day activities. These Centres are accessible to the current students, alumni, faculty/staff including retired person and any other person as per merit and space availability.

In the first phase in 2016, six incubation Centres were set up namely; Indira Gandhi Delhi Technical University for Women (IGDTUW), Netaji Subhas University of Technology (NSUT), Shaheed Sukdev College of Business Studies (SSCBS), Indraprastha Institute of Information Technology and Development (IIITD), Ambedkar University of Delhi and Delhi Technical University (DTU). In the second phase in 2017, five more Incubation Centres were launched; Acharya Narendra Dev College (ANDC), Bhai Parmanand Institute of Business Studies (BPIBS), Delhi Pharmaceutical Science & Research University (DPSRU), Delhi Institute of Tool Engineering (DITE), which replaced College of Arts from the original list and Ambedkar Institute of Advanced Communication technologies and Research (AIACTR).[1-11]

An all out effort was made for the capacity building of stakeholders associated with the Incubators. Standardized operational documents along with the checklist needed for incubators CEO/rent/service/shareholding agreements were prepared and shared. Periodic meetings, knowledge and problem sharing amongst institutions, handholding by TiE led to vibrant collaborations across institutions. Entrepreneurship development activities like ECells, academic programs, workshops, alumni engagement, mentoring, ideathons, workshops, alumni engagement, boot camps etc were organized across all institutions. Operational skills now supplement theoretical knowledge in the institutions.

LITERATURE REVIEW

Startup India is a flagship initiative of the Government of India, intended to build a strong eco-system for nurturing innovation and Startups in the country that will drive sustainable

economic growth and generate large scale employment opportunities. The objective is that India must become a nation of job creators instead of being a nation of job seekers. The Government through this initiative aims to empower Startups to grow through innovation and design.[12]

The entrepreneur has been identified as being disproportionately more important to the success of a firm than their manager counterparts because of the unique challenges they face (and overcome) when engaging innovation (Ensley, Pearson *et al.* 2002). At the same time, business incubation is seen as an effective means of educating and supporting high growth, innovative ventures because "*the desire for individuals to become an entrepreneur and start a business often exceeds their management capabilities*" (Osborne 2000, p.125). Therefore, the business incubator is considered an ideal means of imparting knowledge and skills in an environment that is relevant and immediately effective (the individual learns how to be entrepreneurial and is supported while he or she develops the enterprise) and can be considered as one model of entrepreneurship education. However, there is a lack of consensus, particularly in the higher education environment, about what constitutes a good practice model of entrepreneurship education (Holmgren & From 2005; Matlay & Carey 2007). Further, there are a number of approaches to education which differ in intent and practice (Bérchard & Grégoire 2005). Hindle (2007) suggests that education (at least in the higher education context) should be about philosophy, subject critique and self-critique and this would seem at odds with education that is about solving and overcoming immediate and time pressured challenges and problems associated with new venture formation. A cursory glance at a dictionary definition of the key terms, incubation and education, reveal an underlying difference in meaning that is at the heart of the conflict: to educate is to mentally and morally train while to incubate is to *cause* to develop.[13]

According to the Department of Science and Technology (DST), India has nurtured over 40,000 startups in the last few years and 31 have achieved the Unicorn status. Global Incubation Services (GINSERV) is a state-of-art Technology Business Incubator. It has been promoted by JSS Mahavidyapeetha, Mysore, one of India's largest educational organizations, with the support of National Science & Technology Entrepreneurship Development Board (NSTEDB), Department of Science & Technology, Government of India. Soft-Landing Companies are promoted by NRIs or a foreigner and bring new technologies with an India centric focus. It helps to train Indian manpower in new technology, enable collaborations with local entrepreneurs and bring new knowledge of start-ups to the Incubator.

The components under the scheme include mentoring support in business and technology, networking with other businesses, seed capital assistance, professional assistance to make the enterprise successful and achieve higher growth. Technology based new enterprises are typically characterized as high risk and high growth ventures, and as such, they require an enabling environment like BI to enhance the prospects of success.[14]

India is home to one of the most vibrant startup ecosystems with close to 8000 tech startups, making it the 2nd largest startup ecosystem in the world. Hence, innovation and entrepreneurship is the emerging focus area that is being aggressively promoted to give fillip to the Indian economy. Ministry of Electronics & Information Technology (MeitY), Government

of India is leading and facilitating a gamut of Innovation and IPR related activities across the country towards expansion of this ecosystem. In order to facilitate MeitY's vision of promoting technology innovation, start-ups and creation of Intellectual Properties, a nodal entity called 'MeitY Start-up Hub' (MSH) has been setup under its aegis. MSH will act as a national coordination, facilitation and monitoring centre that will integrate all the incubation centres, start-ups and innovation related activities of MeitY.[15]

METHODOLOGY AND MISSING LINKS OBSERVED

A sincere effort was made to physically visit these Incubation Centres, interact and interview various stakeholders like students, faculty members, incubates, CEOs, companies and their business partners to understand its functioning. Detailed reports were collected to authenticate the claims mentioned on the official websites. The data collected were collated in a tabulated format and analyzed before making an interpretation and coming to conclusions. Some of the observations include:

- *Incubation Fund* – Every host institute received a Government fund through DTTE of Rs 1.5 crore and was to utilize it under Capital Expenditure (Cap Ex), Operation expenditure (Op Ex) and Seed funding. There has been no clarity on what proportion to be used under which head. Some spent over a crore rupees only on infrastructure and found dearth of funds for the operations. The centres had no clarity of funds to be utilized on the promotions, workshops and orientations. In the eventuality, one of the IC procured a grant of over Rs 25 lakhs from GIZ under Indo-German agreement to conduct such events.
- The Government bodies, DSIIDC and PWD were to carry out the infrastructure work which took its own time and charged arbitrary rates. The limited suppliers led to the hike in cost and time factor.
- No fixed yardsticks were framed in allotting the seed fund to the incubatees and it ranged between 1 lakh to Rs 7.5 lakh. Recently, around 15 lakh was given out to one incubate at SSSBS. A seed money of approximately Rs 8.5 lakh was granted to three incubatees, all pass outs from BPIBS.
- Head of the Institute had the decisive power to allot money (incubatees and all expenses), engage manpower (incubatees and recruit staff and board members) and choose the programme (ideas and workshops). This free hand gave room for suspicion and compromise on quality services and appointments.
- Although the incubatees were limited to be a student, alumni, faculty and staff, several outsiders were registered owing to the acquaintance with host institutes. No guidelines have been issued for the engagement of outsiders.
- Incubatees were to capture the market but in the process made a dent inside the institute itself. For example, one of the Incubation Centres imparting training through influence made it compulsory for the students of host institute to undergo training by paying a registration amount of Rs 10,000.
- Board of Directors or Board of Governors were formed to run the Incubation Centres, which is against the company law and had no prior set criteria.

- The salary of CEO varied from 1 lakh to 2.5 lakh and was totally in the hands of Head of the Institute. The Incubation centres would have made a real impact if the CEOs had the subject expertise and a successful business model of their own.
- With no Standard Operating Procedures (SOPs) in place, all the CEOs derived at their conclusions as per their need and convenience.
- No Nodal CEO or an officer was appointed by the Government to facilitate the Incubation Centres collectively. Only for financial applications, they reported to a Joint Director at DTTE. Thus, a guiding factor was missing at the overall functioning of the Incubation Project.
- With the advance of time, the focus drifted from quality to the quantity. The priority of inventing a new product or a new technology shifted towards the number of incubatees engaged. One of the incubation centre considered all the applicants who applied to the tune of 40 as incubatees, although after screening only 8 were registered. The large number had all praises and enabled them to procure the seed money on a priority.

CONCLUSION

The Incubation Centres strive to provide a great opportunity and platform to innovative minds and give right directions to channelize their efforts to succeed further with their business idea. But the lags in Indian ecosystem belie the great objectives of Startup India, these include:

- India's low ranking in '*Ease of Doing Business*';
- Lack of Incubation or startup/seed money to build business in initial phase;
- Lack of infrastructure for new business ventures;
- IPR issues and costs and lack of mentorship and industrial exposure of the graduates and post-graduates.

The new concept of hands on approach over the traditional theoretical study took time to be absorbed against the culture of a practical work for procuring the marks. In the beginning, several faculty members opposed the concept owing to their own job mentality and lack of creativity within themselves. As a result of the mounting pressure and inability to adjust with the changing scenario, the College of Arts which was designated for the IC had to withdraw and instead DITE was listed.

The Incubation centres turned out to be a viable platform for those brilliant ideas which otherwise would not have seen the light of the day. It provided a means for the students pursuing higher studies with a scientific temper to explore their hypothesis and convert their research work into technologies worth for the society. The seed money enabled many of the incubatees to start off on a higher note bypassing the queue and struggle for Bank loans. The hand holding exercise by experts and the industries acted as a lubricant in establishing the ventures by the upcoming entrepreneurs. Entrepreneurship curriculum in Delhi government schools came as a booster for the student community in changing the mindset of the general public. At some places, the seed money was mistaken as loans and the gravity of work was compromised. Revising the course curriculum in accordance with UGC/AICTE being a herculean task, no serious effort was made to be in tune with emerging technologies, latest

business innovations' practices and align to requirement of industries and to introduce course on entrepreneurship development through incubators. Industry experts need to be engaged to teach such frequently updated courses was missing. At times, suitable mentors were not available to help budding entrepreneurs along every step of this application process. Emphasis for mandatory apprenticeship or entrepreneurship could not be put in place and placements played the crucial role for the institutions credibility.

With all these limitations, some of the institutes like DPSRU, IIIT-D and DTU are making all efforts to establish their ICs at the International level with their quality of research work and collaborations. Institutes like DPSRU is harnessing on its unique strengths and capabilities in the research and scientific realm through the development of phytopharmaceutical drugs, cosmeceutics and nano-formulations for various diseases.

The ICs will go a long way with the roping in of more experts, introducing measurable indicators, proper monitoring and above all encouraging the upcoming research fraternity to procure more on the technology as well as business model.

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ANNEXURE I

Table1: Policy Framework

- Each institution to create Section 8 Company and run it professionally with a financially sustainable model;
- Accessible to students, staff, faculty and alumni of the institution;
- Seed funding via debt/equity for registered enterprises set up by incubate after rigorous evaluation;
- Incubation centres to provide shared infrastructure, administrative, legal and technical services and mentoring to all incubates;
- Institutions to foster a culture for innovation, entrepreneurial thinking and enterprise building;
- Institutions to create a dynamic network towards collective problem-solving, collaboration and complementary activity;
- Academic interventions to encourage a culture of entrepreneurship in institutions;
- Updated curriculum including entrepreneurship courses, mandatory apprenticeship and projects;
- Faculty training for promotion of business innovation and start up culture;
- Deferred placements;
- Gap year concept – drop a year for startup.

Table 2: Operationalizing Incubators

- Shaheed Sukdev College of Business Studies
- Netaji Subash University of Technology
- Indira Gandhi Delhi Technical University for Women
- Delhi Technological University
- Indraprastha Institute of Information Technology
- Ambedkar University of Delhi
- Delhi Pharmacecutical Sciences and Research University
- Acharya Narendra Dev College
- Bhai Parmanand Institute of Business Studies
- Delhi Institute of Tools and Engineering
- Ambedkar Institute of Advanced Communication Technology and Research

Table 3: Highlights

- 11 Incubators – largest density of student incubators in the country;
- 43 start-ups initiated, ranging from social entrepreneurship (10), business enterprises (10) to high end technology (23);
- Many incubatee from weaker economic segment;
- Some of the remarkable incubatees include:
  - Khass – Travel Agency employing visually impaired and physically challenged women.
  - Kinara – Roof top framing services managed by displaced farmers from Yamuna belt.
- AirZen – Air quality index monitoring device and analytics platform;
- Movense EN – Creates next-gen 3 D motion photography technology;
- ETI Labs – Internet of Things, Embedded system, Wireless sensor network, Education technology and Automation;
- NatureFab – Sustainable clothing using organic and eco friendly bamboo fabric.
- Steamedu Learning – Fostering curiosity, creativity and imagination in young minds and inculcate 21st century skills and training through S.T.E.A.M.;
- Brand Logos: India, Zenatix, Backpack, Academistic, Coursify, Fasta pesta among many others.

Table 4: Key Activities/Services provided by parent Institute to Incubatees is as follows:

- Mentors support-Workshops/seminars and direct guidance;
- Infrastructural/Facility based services like –office spaces, internet etc.;
- Skill trainings;
- Networking activities;
- Financing/Seed Funds/Access to Venture Capitalists etc.;
- Education/Access to Knowledge related to ideation to concept to validation of product to commercialization;
- Entrepreneurship trainings;
- IPR related support;
- Secretarial Services;
- Hands on working at Entrepreneur Cell.

Table 5: Support system at NSUT IIF

NSUT's internal support system	Intervention taken
Outreach/Sensitization/Culture Development	Electives in entrepreneurship, business conclave, e-summit, technical societies.
Support at Idea generation stage	Lab equipment, mentorship, industry partnership
Support for IPR awareness and Patent Filing	patent support and guidance, government support
Support for Proof of Concept (PoC)	industry partnership for prototyping and feedback
Support for access to existing R & D infrastructure	Labs have the desired equipment and network facility
Exposure to Innovators and Student Startups	Peer to peer guidance available
Collaboration and tie-up with external expert/ organizations	Business conclave, industry seminars, NSIT IIF mentorship and evaluation
Capacity building of stake holders	Peer to peer guidance, industry support

Table 6: Guidelines To Establish Incubation Centres In Educational Institutions

Building the Business Case	Building a strong business case for internal approval and attracting partners and funders is an absolutely crucial step. While long-term financial returns are possibility, it is also useful to highlight the earlier impact and community benefits that can come from accelerating start-ups.
Business retention and job creation	Successful incubator ventures are likely to remain in the local ecosystem, creating opportunities for new job creation as well as channels for university-industry interaction
Increased Tax revenue	A report by the NBIA found that in the US, every 1$ of public investment in incubator translated into $30 in local tax revenue.
Increased Impact Figures	University start-up incubators serve as a pipeline for new student ventures that may not be exploited by traditional technology transfer channels.
Student Recruitment and career Enhancement	Entrepreneurship is increasingly considered an attractive career choice for students. A 2012 survey found that 1/3 of the respondents from the millennial generation were interested in launching their own business.
Alumni Engagement	A software incubator has to have potential to attract both donations from and engagement with alumni. A 2014 QAA report noted that "Entrepreneurial alumni are the main source of donations to universities and are more likely to be inclined to donate if they believe that heir time at University had a material influence on their subsequent entrepreneurial success.

CREATING A CULTURE OF ENTREPRENEURSHIP, START-UPS AND INTELLECTUAL PROPERTY CREATION

- Promote start-ups by creating incubation infrastructure, friendly guidelines for start-up funding, helpful labour law reforms, liberalized guidelines allowing overseas partnering, use of start-up products in government sector, start-up spaces and marketing support programs for start-ups on the basis of preferred Market Access (PMA);
- Changes to current curricula with the aim of developing entrepreneurship in students from schooling days (class X onwards) – "*Catch Them Young*";
- Include entrepreneurship as a subject/add-on course/ elective in Institutions;
- Conduct entrepreneurship boot camps during summer to encourage students participate in entrepreneurial activities;
- Offer start-up founders the option to participate in placement in the year after graduation to increase risk-taking ability;
- Offer incentives to faculty for risk-taking and start-up incubation commercialization of technology;
- Conduct Boot camps for start—ups, Business plan competition etc. where the winners get a chance to utilize the incubation centres being set-up;
- Create entrepreneurship challenges based upon existing problems to foster Innovation;
- Develop a mentorship body to provide support to entrepreneurs; partner with ecosystem players as possible;
- Create entrepreneurship clubs amongst the student and alumni (global/national/local) community.

FACILITATE CREATION OF INCUBATION CENTRES WITHIN THE EDUCATIONAL INSTITUTIONS

- Create a Section 25 company that will act as the holding company for incubators to be created under these guidelines. Multiple companies can be created, Institute/Organisation wise to cover the city/state;
- The holding company will employ professional staff and maintain a small secretariat to support its activities. This will be funded by the government, as per prescribed guidelines issued from time to time;
- The Section 25 (holding) company shall have the budget to create the incubation infrastructure, computing and specialized equipment as needed etc.;
- The holding company shall also create the plans for start-up on boarding, mentoring, growth, fund-raising and exit processes;
- A set of operational guidelines for incubators shall be prepared and each holding company shall be provided the same as best practices.

INFRASTRUCTURE FOR ESTABLISHING AND OPERATING INCUBATORS

- The holding company will enter into an MoU with the participating institute to facilitate setting-up of an incubation centre within the campus.
- The incubator centres in institutions should have a broad based specialization. There could be some natural selection based by the special infrastructure, labs, machines and resources available at the institutions.
- The Institutions that enroll for this program will provide dedicated space to each incubate within their existing buildings and or in the new buildings. A minimum of 5000 sq feet of space is required (10000 sq ft is recommended)
- Each incubator shall have space for meeting rooms, conference facility, open sitting plan offices and limited number of office rooms.
- Infrastructure for tea/coffee/snacks can be created with the pantry/kitchen supplies coming from authorized vendors.
- Incubators should be based on a modular plug and play model with essential infrastructure such as 24 x 7 access, 24 x 7 electricity and back up, internet, LAN, desk tops, telephone connection and instrument, printers, scanners, tea/coffee and rest room facilities, conference/discussion rooms.
- The furniture needs shall be modern, light and functional in keeping with trends at other incubators/accelerators.
- Specialised labs can be made available to incubate companies at terms that can be decided by the management.
- Selected specialist support agencies like advertising, PR, logistics, facilities management can be common for start-ups using this incubation facility to cut operational costs.

SHARED SERVICES TO BE PROVIDED BY INCUBATORS

- Provide a platform where incubatees can easily access services such as accounting, legal services, administrative services, marketing and sales support, etc.
- Incubators should create a panel for regular mentors to provide mentoring and assistance.
- Incubators should establish a panel of visiting guests and experts who can visit once a month/quarter and provide vision and direction to the incubates.

ELIGIBILITY

The incubation centres should be accessible to the current students, Alumni, Faculty/staff including retired person and any other person not belonging to any of the above category may be considered as per merit and space availability, after giving preference to Serial number 1 to 3 categories. On rare to rare case basis, the students of other institutions may also be considered eligible.

SELECTION PROCESS/CRITERIA

- An evaluation process should be put in place to select relevant incubatees for the program;
- Ideas should be assessed through a written application and interview process including detailed technical and financial due diligence. Applications may be shortlisted on certain criteria such as strength and novelty, strength of core business team, funds needed, and time to market. The final selection should be through interview (including a presentation of the business case) by an expert panel consisting of MDs/CEOs of successful start-ups, technical and legal experts along with faculty and investor representatives;
- Special preference and encouragement shall be given to women entrepreneurs and specially-abled entrepreneurs business startups focusing on rural/weaker communities' welfare/transformation under these guidelines. This may include advisory services to create plans to meet the business plan requirements, relaxed conditions for appraisal of business plans and preferred seed funding access subject to availability of resources;
- Mentors may be available to help budding entrepreneurs along every step of this application process.

TRACKING PERFORMANCE

- Create and oversee a reporting mechanism to track performance and success (job creation, revenue, number of incubatees in a year of such centres);
- Tracking of success and failure as the factors leading to both, will help in understanding the usefulness of the centres and provide a knowledge base to up-coming entrepreneurs;
- Business plan evaluation should be done at different stages of the incubation programme.

MENTORSHIP

- A systematic proactive mentorship program must be provided;
- Workshop on mentorship to be conducted;
- Both technical and business mentoring will form part of the incubation program;
- MoUs/tie-ups with the leading trade and industry associations like FICCI, ASSOCHAM, HDCCI, CII and All India Management Association to strengthen the institution-industry interface and access to industry mentors;
- Alumni networks of the institutions and specialist government institutions like bans will be leveraged to act as mentors and business evangelist for the start-ups being incubated;
- Successful ventures will also act as mentors to other start-ups in the same field;
- Provide access to some training workshops aimed at specific business skills such as strategy planning, finance, intellectual property, marketing, HR, operations' innovations,

raising debt and equity finance, etc.;

- Mentors are usually not compensated. If however, the mentorship moves to regular advisory services, the incubatee and the mentor can setup commensurate arrangements including equity, fees, bonus, etc.

ACADEMIC INTERVENTIONS TO FOSTER A CULTURE OF ENTREPRENEURSHIP IN INSTITUTIONS

- Update syllabus :- the institution to revise course curriculum to be in tune with emerging technologies, latest business innovations' practices and align to requirement of industries and to introduce course on entrepreneurship development through incubators. Industry experts need to be engaged o teach such frequently updated courses.
- Faculty training: - A scheme to be developed to train faculty for promotion of business innovation and startup culture.
- Mandatory Apprenticeship: - If apprenticeship is presently part of syllabus and it may also be carried out in any start up including his/her start up.
- Gap year concept: - the institutions to create the concept of student entrepreneur in residence. The outstanding students to be allowed maximum two years of break to pursue entrepreneurship fulltime and this period will not be counted for the time for the maximum time for graduation.
- Innovative and original idea for final year projects:- The nodal incubator to create an online portal with details of all such projects so that student can post their projects on line to avoid duplication.
- Relaxation in academic performance of students:- Relaxation in attendance up to 20% and grace marks of 5 % may be allowed to student start up teams.
- Deferred placement may be allowed to final year students up to 2 years.
- Boot Camps:- Institution entrepreneurship club to be established through incubators to foster innovation and entrepreneurial spirit at Institution level.
- Conductance of seminar / workshop:- Weekend training workshop may be conducted in partnership with leading academies.
- Attracting incubating / startup training institutions International mentors:-The funding provided by Govt may be used for this purpose.
- International start-up culture and exchange program:- Tie up with institutions across globe to be made to encourage start up culture. The world class institutions like Stanford, MIT and Harvard may be approached.
- Networking among Institutions:- A state wide network of institutions to be created with incubator s so that innovators can commercialize their Intellectual property.

FUNDING SUPPORT RECOMMENDATIONS

- The holding company shall have access to grants /soft loans from the Government (state and central) – government to provide seed funding to the start-up in the incubation centres.
- The holding company shall arrange access to SME Micro loan schemes available for state-owned or private banks.
- The holding companies shall provide the funds to create the infrastructure at the educational institutes.
- The holding companies shall pay for the operating expenses of the incubators from the annual budget.
- The institute can approach alumni to create a start-up incubation fund and deploy the funds into the incubate companies.
- The incubator shall organize "Demo days" and VC/funding agency visits aimed at raising investment finance and providing feedback to incubators.
- Most start-ups need seed capital to get off the prototype stage. Many non IT start-ups may need larger seed capital and perhaps even later stage capital to commercialize the idea. The start-up incubation guidelines strongly recommends creation of a seed fund to support early stage investments needed to bootstrap this ecosystem. The fund may be used to acquire minority equity in the venture with reasonable exit clauses that makes the scheme self-sustainable by ploughing back any gains into the program to compensate for investments that may not yield any returns (in keeping with high –risk nature of start-ups)

EXIT

- Entrepreneurs should be allowed to buy back shares at a specified internal rate of return as decided by the institutions and the holding company. If the start-up has risen external funding at some valuation and the external funding agency wants to acquire the incubator shares in addition to the investment, the shares held by the incubator can be acquired at the same value as the investment or at the IRR whichever is higher.
- Exit money should be utilized as per prescribed guidelines of institution. For the holding company, the funds should be ploughed back into the seed fund. The aim of the holding company should be achieved financial break-even through accrued sources in 5-10 years.
- Exit criterion: The incubate companies should leave the incubator, if,
- They have completed the maximum tenure. An extension of 2 months can be given at the end of the 24 months period based on review by the managing board as exceptional case. No extension after 36 months is permitted.
- The growth f the incubate company exceeds the maximum space that is available to be allocated to an incubate.
- Underperformance or un-viability of the business case .

- Incubate meets any of the following criteria
- Enters into an acquisition, merger or amalgamation deal or reorganization deal resulting substantially a change in the profile of the company, its promoters, directors, shareholders, products or business plans, or when a company plans for a public issue.
- Change in promoters /founders team without approval from the centre management.
- Gross indiscipline or unacceptable behaviour towards other incubates companies, incubator staff/officials, service providers or mentors/advisors. Such cases should be reviewed and decided by the holding company management with careful attention to detail.

Table 7: Step by step progress of setting up the Incubation centre

• Creation of Section 8 Company
• Appointment of Board, CEO and other staff in company
• 3. Advertisement to be released and promotional workshops.
• 4. Adequate space made available
• 5. Infrastructure developed
• Interviews for the incubatees appointment and selection
• Expenditure incurred and utilization certificate issued

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