Int. J. Drug Dev. & Res.
| July - September 2014 | Vol. 6 | Issue 3 | ISSN 0975-9344 |
www.ijddr.in

Production Potential of Shikimic acid in Uttarakhand state of India

Silori G. K.[*1]

Pant G. C.[2]

Kumar P[3]

Singh J. K.[4]

Chemical Engineering Department, Kumaon Engineering College, Almora (Uttarakhand), INDIA

Corresponding Authors:
Email:
gauravsilorikec@gmail.com

Abstract:
The present paper examines the production potential of shikimic acid in Uttarakhand state of India as shikimic acid is related to the production of Tamiflu®,one of the most demanding drug of present scenario;an antiviral in treatment of influenza. Information were gathered through literature survey, RTI communication and Targeted group discussion (TGD). The development potential are enormous. These include forest resource,tropical climate, industrial policies, etc. Proper harnessing of these factors will no doubt place Uttarakhand state in a better position to create a vibrant drug hub in the shikimic acid production. Currently shikimic acid is obtained only by Chinese star anise seed (found in china), which is only major source of shikimic acid across the globe and thus scarcity of shikimic acid remains major challenge in the case of any global epidemic. The present studies review and propose the alternative of the problem, in addition to propose proper solution. The paper concludes by proposing some key factorsto assist the objective.

Keywords: Shikimic acid, Tamiflu, Uttarakhand, Development potential, Alternate

1. Introduction:

Shikimic Acid (3, 4, 5-trihydroxy-1-cyclohexene-1-carboxylic acid), a natural organic compound, is an important intermediate in the biosynthesis of lignin aromatic amino acids (phenylalanine, tyrosine, and tryptophan), and most alkaloids of plants and microorganisms. Shikimic acid is generally utilized as a starting material for industrial synthesis of the antiviral *Oseltamivir* (this drug against the H5N1 influenza virus is administered to treat and prevent all the known strains of influenza virus) (1).In the pharmaceutical industry, shikimic acid from the Chinese star anise (*Illiciumverum*) is used as a based material for production of *Oseltamivir* (Tamiflu®). Although Shikimic acid is present in most autotrophic organism, it is a biosynthetic intermediate and in general found in vary low concentrations. The low isolation yield of shikimic acid from the Chinese star anise is blamed for the 2005 shortage of Oseltamivir (2).Currently shikimic acid is obtained only by Chinese star anise seed (found in china), which is only major source of shikimic acid across the globe .Demand of Oseltamivir is increasing day by day as it is used in cure of many influenzas, hence its production in compare to demand is misbalancing. The world is facing huge scarcity of Shikimic acid as there are limited plants/sources are available which contents good amount shikimic acid for industrial purpose.

2. Scope of work:

According to WHO regional influenza pandemic preparedness plan, threats of influenza panefemics will continue to emerge (3, 4) and it will be necessary to develop rapid containment strategies. Tamiflu and other medicines are expected to be crucial in containment strategies (4) such as PanStop 2007 and thus researchers are

active in studying the supply problem for both shikimic acid and Oseltamivir phosphate (5).

It has been reported that the pine needles comprised of 1.5–4.5 % (6, 7) shikimic acid in it. Although a little change with season and age has also been observed. Since pine needles are inexpensive and readily available in North Asia, North America, and Europe, there is a strong potential to provide sufficient quantities for industrial-scale extraction (6).The undermentioned table presents the summery of key selected work done in this regard. The present work is unique and antique of its kind as probably there is no work is available likewise in the regard of SA production. There are more than 115 species of pines are known across the globe (8). Presence of shikimic acid may species wise according to their respective climate topography, geography and others.

2.1 Scope of Work in Uttarakhand:

Uttarakhand is located between 28° 43' – 31° 27' N latitudes and 77° 34' – 81° 02' E longitudes. The river Tons separates the state from Himachal Pradesh in the north- west, whereas the river Kali separates it from Nepal in the east. The greater Himalaya is the northern boundary of the state and is also the international border with China (Tibet). Foot-hills in the south are bound by Uttar Pradesh.Uttarakhand became the 27th state of the Republic of India on 9 November 2000.

Table 1: Summary of literature survey

WORK	PUBLICATION	DESCRIPTION	METHOD	SA % YEILD
Ruohong Sui	Chemical Eng. Tech. 2008	Extraction of Shikimic acid from Scots pine needles (*PinusSylvestris* L.)	Hot-Water Extraction	98
Maine University	Chemistry Monthly Report, 2011	Detection of Shikimic acid in white pine.	NA	NA
JiyunXie, JunfengLan, Lan Yu, and Chunmei Wu	Trans Tech Publication, Switzerland, 2012	Extraction of Shikimic acid from *Pinuselliottii* E. needles	Microwave Pretreatment	95-98
Fengli Chen, KexinHou, Shuangyang Li, YuangangZu, and LeiYang	Hindawi Publishing Corporation, Journal of Analytical Methods in Chemistry, 2014	Extraction and Chromatographic Determination of Shikimic acid in Chinese Conifer Needles with 1-Benzyl-3-methylimidazolium Bromide Ionic Liquid Aqueous Solutions	Ionic Liquids based Ultrasound Assisted Extraction (ILUAE)	99-101
This work	Communicated to IJDDR, 2014	Production potential of Shikimic acid in Uttarakhand state of India	Mentioned	

Major forest types occurring in the State are tropical moist deciduous, tropical dry deciduous, and sub-tropical pine and Himalayan Moist. The recorded forest area of the State is 34,662 km^2, which constitutes 64.79% of its geographic area. By legal status, reserved forests constitute, 71.08%, protected forest 28.51% and unclassed temperate, Himalayan dry temperate, sub-alpine and alpine forest. Forests are largely distributed throughout the state with conifers and Sal being the major forest formations. The State has 6 national parks and an equal number of wildlife sanctuaries covering an area of 0.71 million ha, which constitutes 13.35% of its geographic area. (9)

The famous Corbett Tiger Reserve (CTR) is located in the state covering an area of 0.13 million ha. Nanda Devi Biosphere Reserve (NDBR), having an area of 0.59 million hectare is also located in this state. Uttarakhand supports a large number of

medicinal plants, which are extensively used by the pharmaceutical industry for preparation of drugs used in Indian system of medicine. These plants are either used as single or multi-herb products. (9)

The author's seeks Uttarakhand state as pilot state for consideration by following rational reasons:

☞The Indian Himalayan region (Uttarakhand falls in Himalayan region) alone supports about 18,440 species of plants (Angiosperms: 8000 spp., Gymnosperm: 44 spp., Pteridophytes: 600 spp., Bryophytes: 1736 spp., Lichens: 1159 spp. And Fungi: 6900 spp.) Of which about 45% are having medicinal properties.(10)☞Uttarakhand state is listed one of the five states in India to be declared a world heritage biodiversity site by UNESCO (11).

In addition, rational reason behind preferring Chir pine on other coniferous tree are its:

Abundances☞Chir pine is widely distributed in Uttarakhand state (Mainly hilly regions), The RTI correspondence held between government of India and author confirms that Uttarakhand state has finest Chir pine forest across the country with *ca.* 20% Chir pine forest (12). (Shown in Table)*Accessibility*☞Chir pine forest are distributed in Sub-Himalayas (altitude range 300-1000m) and Mid-Himalayas (altitude range: 1000-3000) hence becomes easily accessible (8,9)

Biodiversity☞Some species namely *Andrographispaniculata, Mucunapruriens, Spilanthesacmella* and *Solanumkhasianum* can grow easily under Chir pine forest which are also recommended for medicinal and aromatic purpose hence adding extra benefits in the current scenario. (13)

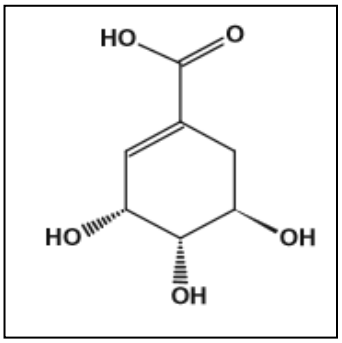

Figure 1: Shikimic acid structure

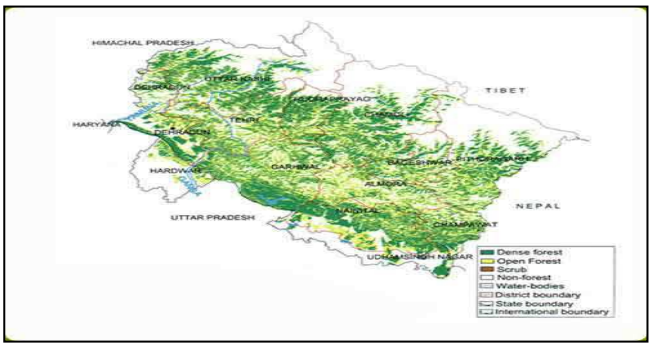

Figure 2: Forest in Uttarakhand

Table 2: Chir pine distribution in various states of India

Sl. No	State-UT	Chir pine area with RFA	RFA as in ISFR 2011	Chir pine forest (%)
1.	Himachal Pradesh	3082.94	37,033	8.32
2.	Jammu & Kashmir	3366.60	20,230	16.64
3.	Punjab	69.51	3,084	2.25
4.	*Uttarakhand*	6904.02	34,651	19.92

Source: *RTI Communication, NFDMC, Ministry of Environment and Forest, Government of India.*

3. METHODLOGIES:

3.1Experimental analytical review:

Sofar we have discussed the production potential of shikimic acid in Uttarakhand, the foremost major challenge of the work remains: quantity of shikimic acid extracted and is that aforesaid procedure is economical. Hence we proceed to undermentioned section as if both above mentioned conditions in this section are favorable to us. A demo plant could be established to see pros and cons in this regard, if output is not desirable it could be adjourned till further modification.

3.2 Selection of pilot places:

All the districts in the country have been classified into four categories:

1) No industry districts a 'special region' districts, 2) Moderately backward districts 3) Least backward districts and 4) Non-backward districts (14). The A, B and C category are eligible inter-alia for subsidy on investment in fixed assets in an industrial unit, as given below:

1) A: 25 lakh 2) B: 15 lakh 3) C: 10 lakh 4) D: Not eligible for subsidy (14).The hilly districts of Uttarakhand are primarily focused for plant establishment as they are rich in raw material as well as they falls under creamy category which are mentioned above. The selection of these pilot places were done considering geography, transportation, raw material feasibility etc. Furthermore selection of pilot plant places were finally done by SWA (Strength and Weakness Analysis) and Uttarakhand development policy 2008. The name of places are listed district wise in Table 3.

DISTRICT	Avg. Altitude in m	PLACES
PauriGarhwal1650		
Chamoli	1293	Gairsen, Tharali, Pharsawn
Uttarkashi	1158	Dunda, Barkot, Khal
Almora	1651	Bhikiyasen, Chaukhutiya, Daniya
Bageshwar	1004	Baijnath, Kapkot, Bageshwar
Pithoragarh	1514	Askot, Rameshwar, Nachani

Table 3: Places for pilot plant establishment

3.3 Production plant design:

The undermentioned figure shows the process the plant establishment which is limited toflow diagram 3. The economic estimation of plant was challenging as there is no plant running across the country on the same regard hence adjourned for design seekers.

3.4 Price components and cumulative mark-up:

The study represents the price estimation of product as it will add more revenue in the Govt. GDP .Retail price of medicines in India is determined by the pricing norms promulgated in the Drug Prices Control Orders (DPCO) of the Government of India, the taxes levied by the central and state governments (e.g. central and state sales taxes) and the profit margins levied at successive tiers in the trade channels.

The prevalent formula used for price determination is:

RP = (MC + CC + PM + PC) X (1 + MAPE/100) + ED (15)

Where, RP is Retail price

MC is Material cost (includes cost of the active pharmaceutical ingredients

And excipients used) CC is Conversion cost

PM is Packing materials cost

PC is packing charges

Covered in Scopus & Embase, Elsevier Int. J. Drug Dev. & Res., July - September 2014, 6 (3): 280-285

MAPE is Maximum allowable post-manufacturing expenses (not to exceed 100% for indigenously manufactured formulations)

ED is Excise duty charged by the central government (16% at the current time).

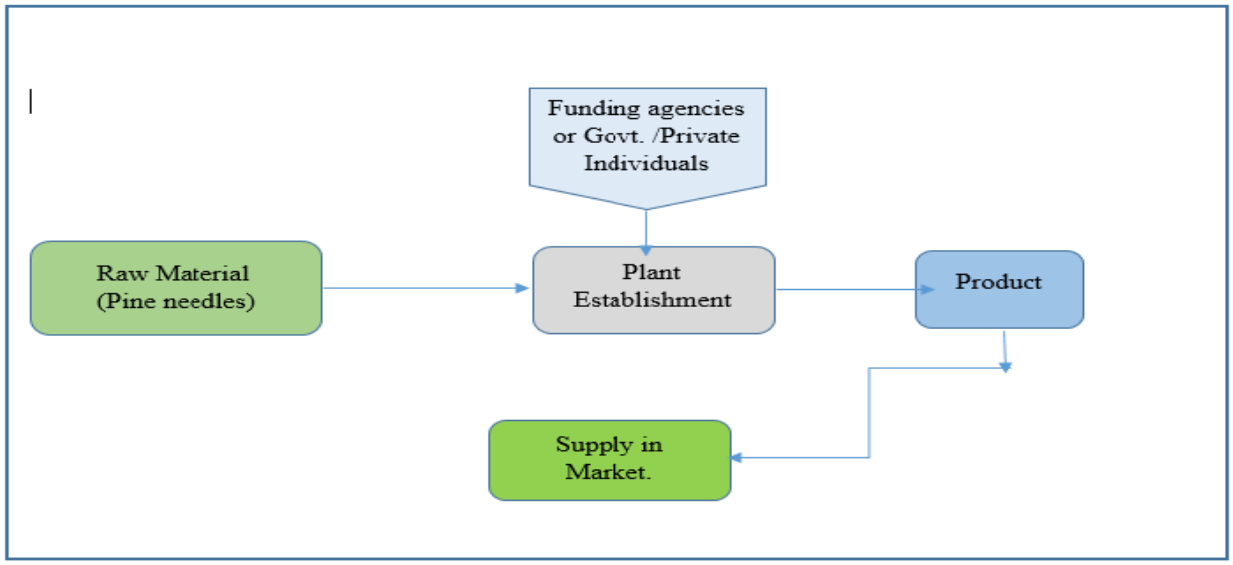

Figure 3: Figure representation of plant establishment

3.5 Major challenges:

So far we have discussed many possibilities in the favor of development regards. There exits limitations too, which varies from low capital base,unavailability of high quality of inputs, less innovation actions , lack of proper market information to low level of research and development , inadequate accession to the monetary institutions less exposure to international environment and lack of professionalism.

4. Discussion & Conclusion:

In this report, we have exposed to limelight the development potential and the medicinal opportunities that exist in Uttarakhand state of India for both the government and the enterprising individuals. The work has some limitations i.e., lack of analytical data, plant economy estimation. New and better techniques for industrial production of shikimic acid should be emphasized. However analyzing enough merits as well demerits, the authors strongly recommends Uttarakhand state as a pilot plant district for the shikimic acid development and production.

Acknowledgment:

The authors are thankful to Dr. R S Rana; Director, Centre for Higher Education and Training and Dr. J B Kandpal; Head, Research and Development, Indian Glycols Ltd. For their kind review. Government of Uttarakhand and Govt. of India is thankfully acknowledged for providing needful data.

References:

1) Denis V. Bochkov, Sergey V. Sysolyatin, Alexander I. Kalashnikov & Irina A. Surmacheva "Shikimic acid: review of its analytical, isolation, and purification techniques from plant and microbial sources", J ChemBiol (2012) 5:5–17
2) http://en.m.wikipedia.org/wiki/Shikimic_acid

3) WHO, Regional Influenza Pandemic Preparedness Plan (2006-2008). World Health Organization, New Delhi, 2006.
4) WHO, Epidemic and Pandemic Alert and Response (EPR), http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_02_19/en/index.html .World Health Organization, 2007
5) Hiroki Ohira, Naota Torii, Taku M. Aida, Masaru Watanabe and Richard L. Smith Jr. "Rapid separation of Shikimic acid from Chinese Star Anise (*Illiciumverum* Hook f.) with hot water extraction. Separation and Purification Technology 69 (2009) pp.102-108
6) R. Sui "Extraction of shikimic acid from pine needles". Chem. Eng. Technol. 2008, 31, No. 3, 469–473, 2008
7) Fengli Chen, KexinHou, Shuangyang Li, Yuangang Zu, and LeiYang, "Extraction and Chromatographic Determination of Shikimic Acid in Chinese Conifer Needles with 1-Benzyl-3-methylimidazolium Bromide Ionic Liquid Aqueous Solutions", Hindawi Publishing Corporation Journal of Analytical Methods in Chemistry Volume 2014, Article ID 256473, 12 pages.
8) http://en.m.wikipedia.org/wiki/pine
9) Uttarakhand State Perspective and Strategic Plan 2009-2027, Watershed Management Directorate, Dehradun
10) http://forest.uk.gov.in/
11) http://sbb.uk.gov.in/
12) RTI communication, Govt. of India to Gaurav Kumar Silori (corresponding author), No. 22-284/2013-NFDMC; May 30, 2013.
13) An Introduction of Medicinal and Aromatic Plants in Chir Pine (*PinusRoxburghii*) Forest of India: A Sustainable Technique. 2011 2nd International Conference on Environmental Science and Technology IPCBEE vol.6 (2011) © (2011)IACSIT Press, Singapore
14) Backward Areas and Industrial Policy by Sree Rama Rao, December 2008, www.citeman.com/4640-backward-areas-and-industrial-policy.html
15) Report on "Medicine Prices and Affordability in the State of West Bengal, India" by Prof. Santanu Kumar Tripathi, Ms. Dalia Dey and Dr. AvijitHazra.

Article History: ----------
Date of Submission: 16-09-2013
Date of Acceptance: 29-09-2013
Conflict of Interest: NIL
Source of Support: NONE