Occurrence of taraxerol and taraxasterol in medicinal plants

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ABSTRACT

Indian soil germinates thousands of medicinal drugs that are cultivated with a purpose to obtain a novel drug. As it is a well-established fact that the structural analogs with greater pharmacological activity and fewer side-effects may be generated by the molecular modification of the functional groups of such lead compounds. This review throws light on two natural triterpenes - Taraxerol and Taraxasterol which have many important pharmacological actions including anti-cancer activity, their chemistry, biosynthesis aspects, and possible use of these compounds as drugs in treatment of cancer. A silent crisis persists in cancer treatment in developing countries, and it is intensifying every year. Although at least 50-60% of cancer victims can benefit from radiotherapy that destroys cancerous tumors, but search for the paramount therapy which will prove to be inexpensive with minimal side effects still persists. Various treatment modalities have been prescribed, along with conventional and non-conventional medicine but due to their adverse effects and dissatisfaction among users, these treatments are not satisfactory enough to give relief to patients. Hence, this review sparks the occurrence of Taraxerol (VI) and Taraxasterol (VII) in nature, so that the natural godowns may be harvested to obtain these potent compounds for novel drug development as well as discusses limitations of these lead compounds progressing clinical trials.

Key words: Plant tissue culture, taraxerol, taraxasterol

INTRODUCTION

Nowadays, bioactive agents from natural sources are discovered and screened for their therapeutic efficacy. Natural products are known to account for 30% of international drug sales. Although most of the medicines are derived from terrestrial plants and animals, ecologists estimate the number of the species in the marine environment to be 0.5-10 million.[1] Most of these are still on the verge to be discovered. Well, that may be the reason behind therapeutic efficacy of natural products being predominantly achieved in antibiotic therapies, oncology, and immune regulation. Natural products are generally not related to the biological environment of the producing organism, henceforth it is less likely to identify potent natural products against molecular targets. Furthermore, higher hit rates are generally obtained for natural product libraries in high throughput screening campaigns (HTS) compared to medchem or combichem libraries. Certainly, natural products are a valuable source of unsurpassed structural diversity and functional density to identify screening hits. After a long period, natural products drug discovery has again gained attention. Also, World Health Organization (WHO) has been promoting traditional medicines as a source of less expensive, comprehensive medical care, especially in developing countries. However, despite the promise of these alternative drug discovery methods, there is still a shortage of lead compounds progressing into the clinical trials. This is specially the case in therapeutic areas such as oncology, immunosuppression, and metabolic diseases where natural products have played a central role in drug discovery.

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BIOSYNTHETIC ASPECTS

The biosynthesis of taraxerol (VI) is same up to formation of squalene to (3S)-2, 3-epoxy-2, 3-dihydrosqualene biosynthesis as in the biosynthesis scheme of triterpenes by enzymes oxidosqualene cyclases. After this, (3S)-2, 3-epoxy-2, 3-dihydrosqualene gets converted to olean-13-yl cation, which is further converted to taraxerol by the action of enzyme taraxerol synthase Systematic name: (3*S*)-2, 3-epoxy-2, 3-dihydrosqualene mutase (cyclizing,

taraxerol-forming). The enzyme gives taraxerol, β-amyrin, and lupeol in the ratio 70:17:13. Also the olean-13-yl cation undergoes a series of rearrangement reactions to give isomultifluorenol, ψ taraxasterol, and taraxasterol (VII) [Figure 1].[2]

Chemistry

The CAS name of Taraxerol, Figure 2a is (3b)-D-Friedoolean-14-en-3-ol. Its additional names include isoolean-14-en-3b-ol, skimmiol, alnulin, tiliadin. Its molecular formula is $C_{30}H_{50}O$ and molecular weight is 426.72. Its melting point is 282-285°C. Its structure was given by Beaton *et al.*[3] The CAS name of Taraxasterol, Figure 2b is (3b, 18a, 19a)-Urs-20 (30)-en-3-ol. Its molecular formula is $C_{30}H_{50}O$ and molecular weight is 426.72 same as Taraxerol. Its structure and configuration was reported by Ames *et al.*[4] The insecticidally inactive substance pyrethrol from pyrethrum flowers has been identified as taraxasterol.[5] Both Taraxerol and Taraxasterol were investigated by high-performance liquid chromatography (HPLC) using methanol containing 0.1% phosphoric acid.[6] A simple and precise high-performance thin layer chromatography (HPTLC) method has been developed for estimation of Taraxerol with hexane and ethyl acetate (80:20 v/v), using visualizing agent anisaldehyde sulphuric acid, and scanning of plate was done at 420 nm. The system was found to give compact spots for Taraxerol (R_f 0.53).[7]

Pharmacological actions

Taraxerol and taraxasterol are important compounds that possess anti-tumor actions.[8] Taraxerol showed significant anti-inflammatory activity in albino rats as well as anti-cancer activity against sarcoma 180 cell line in mice.[9] Both compounds showed remarkable inhibitory effect on mouse spontaneous mammary tumors.[10] Triterpenes are also known to augment the inhibitory effects of anti-cancer drugs.[11] Also it has been known to benefit in Alzhiemer's and Parkinsonism.[12] Taraxerol is known to induce apoptosis, COX inhibitor,[13] acetyl cholinesterase inhibitor,[14] and possess anti-microbial potential.[15] Taraxasterol is anti-allergic,[16] anti-oxidant,[17] and anti-inflammatory.[18] Taraxerol is also known to benefit in diabetes.[19] Both the compounds are also known to exhibit activity against snake venom.[20] Table 1, below, enlists medicinal plants containing taraxerol and taraxasterol.

LIMITATIONS AND FUTURE PROSPECTS

Although there are many lead compounds with promising potential for cancer therapy, the cytotoxicity would itself become a constraint for this because most of these compounds could be cytotoxic towards normal cells in addition to the cancerous cells. Various researches have been carried out on both these

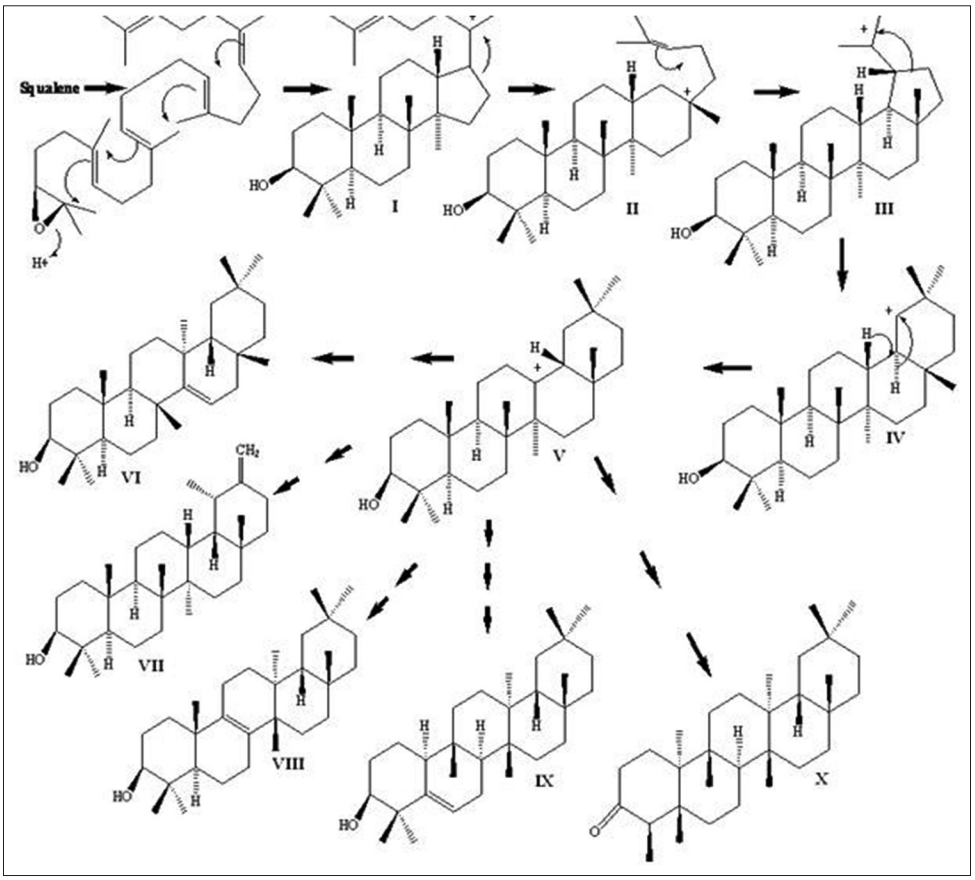

Figure 1: Biosynthetic pathways followed by Taraxasterol and Taraxasterol: Sqaualene act as a precursor molecule lead to formation of (3S)-2, 3-epoxy-2, 3-dihydrosqualene (I), dammarenyl cation (II), baccharenyl cation (III), lupanyl cation (IV), and olean-19-yl-cation (V), olean-19-yl-cation further forms taraxerol (VI), taraxasterol (VII), iso-mumultiflurenol (VIII), glutinol (IX), and friedelin (X)

Table 1: List of medicinal plants containing taraxerol and taraxasterol

Name of plant	Constituent	Part containing active constituent	Reference
Mangifera indica (Anacardiaceae)	Taraxerol	Aerial parts	[19]
Taraxacum japonicum (Compositae)	Taraxerol and taraxasterol	Roots	[10]
Achillea millefolium (Asteraceae)	Taraxerol and taraxasterol	Leaves	[21]
Acrocarpus fraxinifolius Wight and arn (Caesalpiniaceae)	Taraxerol and taraxasterol	Seed oil	[22]
Bauhinia retusa Roxb. (Fabaceae)	Taraxerol and taraxasterol	Seed oil	
Catharanthus roseus L. (Apocyanaceae)	Taraxasterol and taraxerol	Seed oil	
Casuarina equisetifolia L. (Casuarinaceae)	Taraxasterol and taraxerol	Seed oil	
Mimusops elengi L. (Sapotaceae)	Taraxasterol and taraxerol	Seed oil	
Mimusops hexandra Roxb. (Sapotaceae)	Taraxasterol and taraxerol	Seed oil	
Nymphaea nelumbo L. (Nymphaeceae)	Taraxasterol and taraxerol	Seed oil	
Prosopis juliflora (Sw.) (Fabaceae)	Taraxasterol and taraxerol	Seed oil	
Pongamia pinnata (Fabaceae)	Taraxasterol and taraxerol	Seed oil	
Alnus glutinosa (L.) Betulaceae	Taraxerol	Bark	[23]
Butyrospermum parkii (Sapotaceae)	Taraxerol and taraxasterol	Shea butter from seed kernels	[24]
Bryophyllum pinnatum (Crussulaceae)	Taraxasterol and taraxerol	Aerial parts	[25]
Befaria racemosa (Vent.) Ericaceae	Taraxerol	Bark	[26]
Tilia cordata Mill Tiliaceae	Taraxerol	Bark and roots	
Litsea dealbata Nees, (Lauraceae)	Taraxerol	Aerial parts	
Centipeda minima (Asteraceae)	Taraxasterol	Leaves	[12]
Camellia jonica L. (Theaeaceae)	Taraxerol and taraxasterol	Seed oil	[27]
Thea sinensis L. (Theaceae)	Taraxerol and taraxasterol	Seed oil	
Phytolacca Americana L. (Phytolaccaceae)	Taraxasterol and taraxerol	Seed oil	
Calendula officinalis (Compositae)	Taraxasterol and taraxerol	Flowers	[28]
Carthamus tinctorius (Compositae)	Taraxasterol and taraxerol	Flowers	
Chrysanthemum morifolium (Compositae)	Taraxasterol and taraxerol	Flowers	
Cosmos bipinnatus (Compositae)	Taraxasterol and taraxerol	Flowers	
Helianthus annus (Compositae)	Taraxasterol and taraxerol	Flowers	
Matricaria matricarioides (Compositae)	Taraxasterol and taraxerol	Flowers	
Cyanara cardunculus L. (Artichoke) (Compositae)	Taraxasterol and taraxerol	Flowers	[29]
Carthamus lanatus (Asteraceae)	Taraxasterol and taraxerol	Aerial parts	[30]
Calotropis procera (Asclepediaceae)	Taraxerol	Aerial parts	[31]
Clitorea ternatea (Fabaceae)	Taraxerol	Leaves and roots	[7]
Coccinia indica (Cucurbitaceae)	Taraxerol	Leaves and roots	[32]
Euphorbia tirucalli (Euphorbiaceae)	Taraxerol and taraxasterol	Latex and stem	[33]
Ficus carica (Moraceae)	Taraxasterol	Aerial parts	[34]
Momordica charantia (Cucurbitaceae)	Taraxerol	Fruits	
Pteleopsis myrtifolia (Combretaceae)	Taraxerol	Leaves	
Ficus glomerata (Moraceae)	Taraxerol	Leaves	[35]
Ficus racemesa (Moraceae)	Taraxerol and esters of taraxasterol	Latex and fruit	[36]
Hieracium pilosella L. (Asteraceae)	Taraxerol and taraxasterol	Rhizomes	[37]
Hypericum perforatum (Hypericaceae)	Taraxasterol and taraxerol	Aerial parts	[38]
Mikania cordifolia (Asteraceae)	Taraxasterol	Aerial parts	[39]
Nigella sativa (Ranunculaceae)	Taraxerol	Seeds	[40]
Olea europaea (Oleaceae)	Taraxasterol and taraxerol	Aerial parts	[41]
Philadelphus coronarius L. (Hydrangeaeceae)	Taraxerol and taraxasterol	Twigs	[42]
Struthanthus marginatus (Loranthaceae)	Taraxerol	Aerial parts	[43]
Struthanthus concinnus (Loranthaceae)	Taraxerol and taraxasterol	Leaves	
Strobilanthes callosus Nees (Acanthaceae)	Taraxasterol and taraxerol	Aerial parts	[44]
Taraxacum officinale Webers (Compositae, Asteraceae)	Taraxerol and taraxasterol	Roots	[45]
Taraxacum mongolicum (Compositae)	Taraxerol and taraxasterol	Roots	[46]
Taraxacum platycarpum (Compositae)	Taraxasterol and taraxerol	Roots	[47]
Solanum lycopersicum (Solanaceae)	Taraxerol and taraxasterol	Fruit and leaves	[2]

compound's anti-cancer activity on animal cell lines but further researches must be carried out to find out the effect of these compounds on human cancer cell lines and specificity of these compounds on cancer cells. Also, the research must be carried out to ascertain the possible mechanism of action of both these compounds as no satisfactory data is available for mechanism of anti-cancer activity of these compounds as well as their adverse effects must be also assessed. Therefore, considerable cytotoxicity studies must be conducted employing the lead compounds before introducing them to drug development phase. However, advances in drug delivery systems could be applied effectively in specific delivery of therapeutics. Cancer cells carry

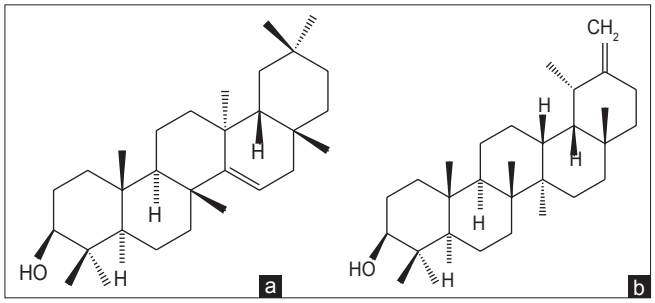

Figure 2: (a) Structure of Taraxerol (3β;)-D-Friedoolean-14-en-3ol) (b) Structure of Taraxasterol (3β; 18α; 19α;)-Urs-20(30)-en-3-ol)

specific receptors that are expressed at higher levels than their normal counterparts. Often these receptors have binding affinity towards specific proteins or peptides and these can be used for direct targeting of cancer cells which is effectively applicable to develop targeted delivery systems. Nano drug carriers coated with cancer cell receptor binding factors are novel and effective approach for the targeted delivery of drugs. This method can be used to deliver anti-cancer triterpenols to the cancer tissues and thereby protecting the normal adjacent tissue cells.[48] Moreover, the possibility of continous supply of the product and the ecological importance of the triterpene sources are factors of importance before entering the drug development phase. Sustainable production of these compounds through chemical synthesis or isolation must be ensured. The structural complexities have challenged the chemical synthesis and thus it would be a limitation to the entering of these compounds to the drug development phase. However, with the advances in synthetic chemistry and an understanding of the biosynthetic pathway of triterpenes newer opportunities for exploitation of these compounds as drug leads are opening up.[49]

CONCLUSION

Plant tissue culture science has recently reported various elite gemplasms which constitutes high amount of therapeutically active compounds then its native form. Lower native concentration of taraxerol and taraxasterol limits its applications in pharmaceutical science. Tissue culture science has successfully explored various germplasms to manipulate the *in vitro* conditions for elevating the concentration of these compounds in their native form. Anticancer and other potential properties of these compounds attracted tissue culture science to explore various strategies to trigger their concentration and trace their respective pathways for provoking their utilization in the therapeutic world. Optimization/manipulation of *in vitro* conditions, tracing biosynthetic pathways, elicitation, precursor feeding, immobilization, and genetic manipulation still holds promises in understanding the facts that hinders native synthesis of such biomarker compounds. Nevertheless, of significant challenges remain: Cancer still remains to be a disease of unknown etiology and none of the therapies described represents a cure. It will be interesting to see whether the progress in Indian herbs to generate novel formulation will eventually provide the profound insights required to conquer this condition for the next 25 years.

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