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STIGMASTEROL: A COMPREHENSIVE REVIEW

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ABSTRACT

Extensive research has been carried out from last decades to discover potential constituents from plant sources. Stigmasterol is an important constituent and has been isolated from plants. It is involved in the synthesis of many hormones like progesterone, androgens, estrogens and corticoids. In addition to stigmasterol many of its derivatives like, spinasterol, fucosterol, cyasterone, stigmasterol glucoside, fucosterol epoxide, stigma-4en-3one, 29-fluorostigmasterol etc. have been isolated and their pharmacological aspects has been assessed. This comprehensive account provides information about stigmasterol and its derivatives. The diversity in their pharmacological reports reveals that this constituent is worth further investigation.

INTRODUCTION: Stigmasterol, also known as Stigmasterin or Wulzen anti-stiffness factor (**Figure 1**), an unsaturated plant sterol present in various medicinal plants. Stigmasterol is utilized in a number of chemical processes which are designed to yield numerous synthetic and semi-synthetic compounds for pharmaceutical industry. It acts as a precursor in the synthesis of progesterone and acts as an intermediate in the biosynthesis of androgens, estrogens, corticoids [1] and in the synthesis of vitamin D_3 [2].

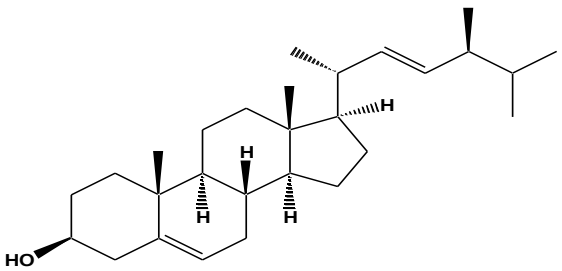


FIG. 1: STRUCTURE OF STIGMASTEROL

It was first isolated in Calabarbohne in 1906 by Adolf Wind Form and A. Hauth [3]. Further, it has been isolated from various medicinal herbs like *Croton sublyratus* [4], *Ficus hirta* [5], *Eclipta alba* (L.) *Hassk* [6], *Eclipta prostrate* [7], *Parkia speciosa* [8], *Gypsophila oldhamiana* [9], *Eucalyptus globules* [10], *Aralia cordata* [11], *Emilia sonchifolia* [12], *Akebia quinata* [13], *Desmodium styracifolium* [14], *Heracleum rapula* [15] etc.

Stigmasterol has been investigated for its pharmacological prospects such as antiosteoarthritic, antihypercholestrolemic, cytotoxicity, antitumor, hypoglycaemic, antimutagenic, antioxidant, anti-inflammatory and CNS effects.

Chemistry: Stigmasterol is chemically, (3S, 8S, 9S, 10R, 13R, 14S, 17R)-17-[(E, 2R, 5S)-5-ethyl-6-methylhept-3-en-2-yl]-10, 13-dimethyl-2, 3, 4, 7, 8, 9, 11, 12, 14, 15, 16, 17-dodecahydro-1Hcyclopenta[a]phenanthren-3-ol has been isolated and its presence was confirmed by performing some reactions like Salkowski and Liebermann Burchard reaction [16] and structure of stigmasterol was elucidated by IR and NMR. As it is non-polar in nature, it is isolated from various parts of the plants by extracting with solvents which are higher in the ellutropic series i.e., non-polar solvents only.

It has been found in the petroleum ether extract of aerial parts of *Ageratum conyzoides* (Asteraceae) [17], *Calotropis gigantean* [18], root and aerial part of *Desmodium gangeticum* [19], seeds of *Terminalia chebula* [20], petroleum ether extract of aerial parts of *Byrophyllum pinnatum* [21], petroleum ether extract of woody stem of *Abelmoschus manihot* [22], hexane extract of leaves of *Pandanus amaryllifolius* [23].

Biosynthesis of phytosterol from mevalonate and deoxy-xylulose pathway was investigated in the callus culture of *Croton sublyratus* from the leaf explants. It was found that biosynthesis was active during the linear phase of the culture and both pathways contribute equally. Feeding of [1-^{13}C] glucose into the callus culture at this growth phase showed that the label from glucose was highly incorporated into both phytosterols. Isolation of the labelled products followed by ^{13}C NMR analysis revealed that the phytosterols had their ^{13}C-labeling patterns consistent with the acquisition of isoprene units via both the mevalonate pathway and the deoxy-xylulose pathway with relatively equal contribution. Since the biosynthesis of phytosterol has so far been reported to be mainly from the classical mevalonate pathway, this study provides new evidence on the biosynthesis of phytosterols via the novel deoxy-xylulose pathway [4].

Diagrammatic representation of the pathway is shown in **Figure 2**.

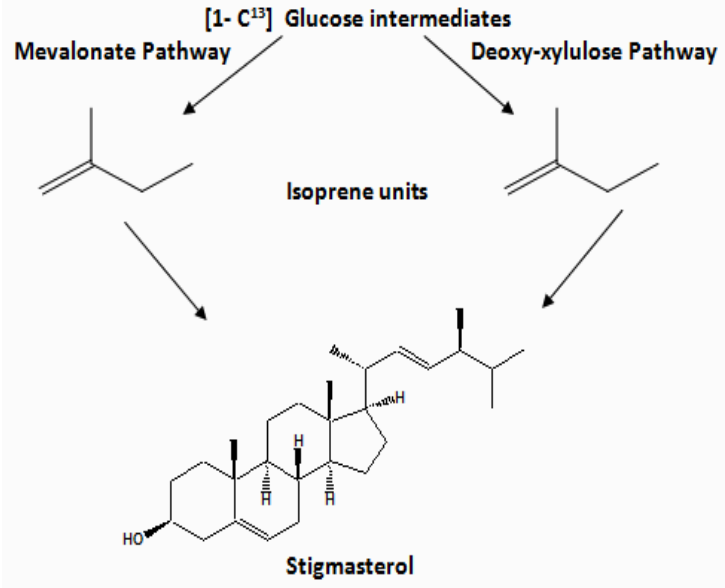
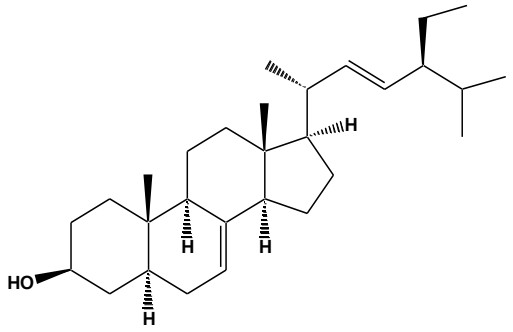


FIG. 2: DIAGRAMMATIC REPRESENTATION OF BIOSYNTHETIC PATHWAY OF STIGMASTEROL IN *CROTON SUBLYRATUS*

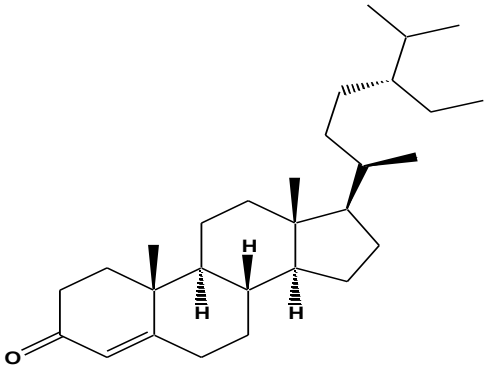
Apart from stigmasterol a number of its derivatives have also been isolated from plants and their pharmacological aspects evaluated. These derivatives along with their pharmacological activities are listed in **Table 1** and their structures are shown in **Figure 3**.

TABLE 1: DERIVATIVES OF STIGMASTEROL AND THEIR PHARMACOLOGICAL ACTIVITIES

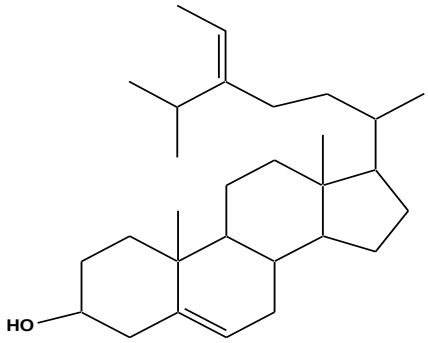
Derivative	Pharmacological Activity	Reference
Cyasterone	Anti feeding [24]	Courgeon AM (1972) [25]
Fucosterol	Antioxidant,[26] Antidiabetic [27]	Minale L, *et al.* (1977) [28]
Foetidin	Hypoglycaemic	Marguis VO (1977) [29]
Stigmast-5-ene-3 beta, 28-diol	---	Nicotra F (1979) [30]
Stigmast-5-en-3 beta, 24-diol	---	Nicotra F (1979) [30]
Fucosterol epoxide	Insecticide [31]	Fujimoto Y (1980) [32]
Spinasterol	Anti-tumour [33]	Yasukawa K (1981) [34]
29-fluorostigmasterol	Insecticide	Prestwich GD (1984) [35]
Stigmasterol-24,28-epoxide	---	Svoboda JA (1989) [36]
Dehydrooogoniol	Female activating hormone [37]	Svoboda JA (1989) [36]
3-O-(6'-O-palmitoylglucosyl)stigmasta-5, 25(27)-diene	Antimutagen	Guevara AP (1990) [38]
3-O-(6'-O-stearoylglucosyl)stigmasta-5, 25(27)-diene	Antimutagen	Guevara AP (1990) [38]
3-hydroxystigmast-5-en-7-one	Anticomplementary	Ebihara T (1991) [39]
22, 23-dihydrospinasterone	---	Ding L (1991) [40]
6-chlorostigmasterol	---	Chen WX (1993) [41]
Stigmasta-5, 22-dien-3-ol	---	Ruan J (2001) [42]
Stigmasterol glucoside	Neurotoxic	Khabazian I, *et al.* (2002) [43]
12-hydroxystigmast-4-en-3-one	Cytotoxic	Chowdhary R (2003) [44]
(24R)stigmast-1, 5-dien-3 beta-ol	Antioxidant, antimicrobial [45]	Ali A (2003) [46]
Stigmast-4-en-3-one	Hypoglycaemic	Alexander-Lindo RL (2004) [47]



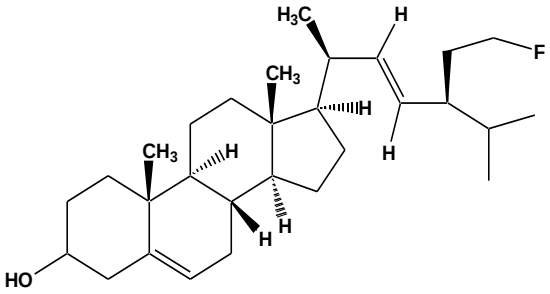
SPINASTEROL



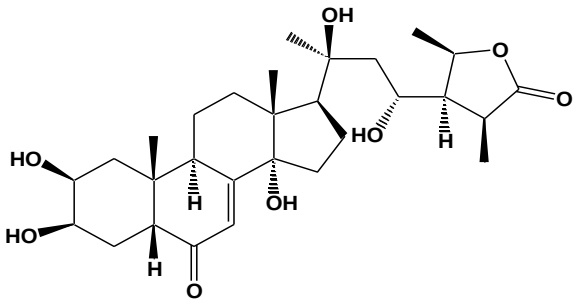
STIGMASTAN-4EN-3ONE



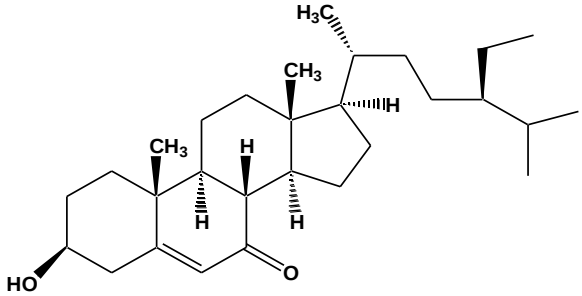
FUCOSTEROL



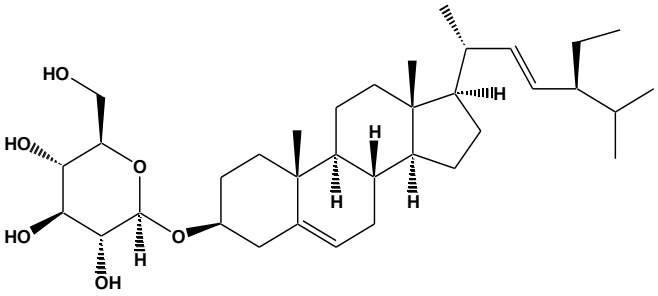
29-FLUORO STIGMASTEROL



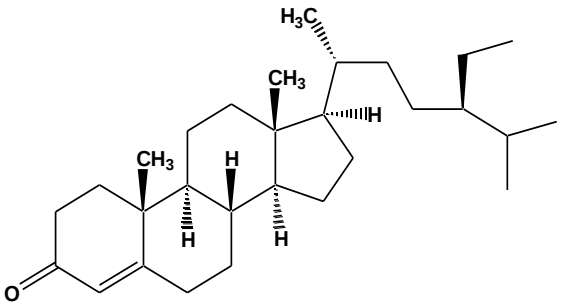
CYASTERONE



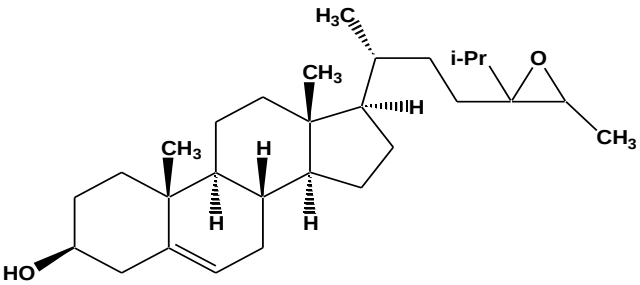
3-HYDROXYSTIGMAST-5-EN-7-ONE



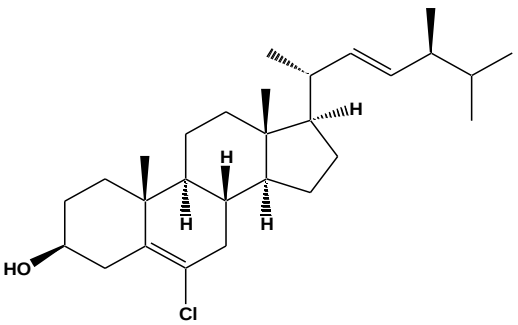
STIGMASTEROL GLYCOSIDE



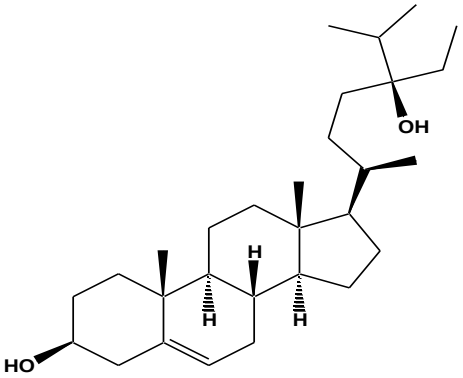
12-HYDROXYSTIGMAST-4-EN-3-ONE



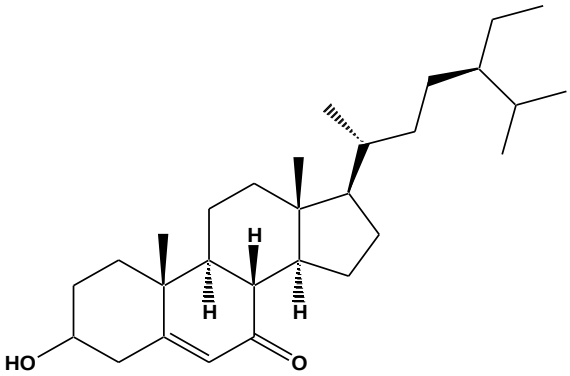
FUCOSTEROL EPOXIDE



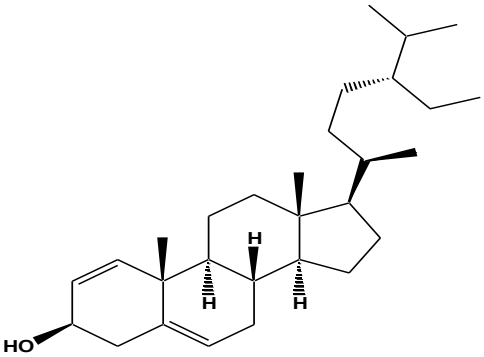
6- CHLORO STIGMASTEROL



STIGMAST-5-EN-3 β, 24-DIOL



3-HYDROXYSTIGMAST-5-EN-7-ONE



(24R) STIGMAST-1, 5-DIEN-3 β-OL

Figure 3: Structures of derivatives of stigmasterol.

PHARMACOLOGICAL STUDIES OF STIGMASTEROL

Anti-osteoarthritic activity: Stigmasterol was investigated by Gabay O, for its antiosteoarthritic activity. Newborn mouse chondrocytes and human osteoarthritis chondrocytes were incubated for 18 hour with or without IL-1β. Then these cells were incubated for 48 hour with stigmasterol and the results were compared to the untreated cells. Expression of various genes involved in the cartilage turn over, MMP-3, MMP-13, and ADAMTS-4, was elevated after treatment with IL-1beta for 18 hour and stigmasterol significantly decrease this effect and hence produces anti-osteoarthritic effect [48].

Anti-hypercholestrolemic activity: It was found by Chandler RF that stigmasterol has significant effect on serum cholesterol comparable with the antihypercholestrolemic activity of β-sitosterol. So, this study concluded that saturation of the side chain, at least at C22 is important for antihypercholestrolemic activity [49]. Further, Batta AK found that this plant sterol has been found to compete with cholesterol for intestinal absorption and thus lower the plasma concentration of cholesterol. Stigmasterol was reported to inhibit cholesterol biosynthesis via inhibition of sterol Δ_{24}-reductase in human Caco-2 and HL-60 cell lines thus suppressing hepatic cholesterol [50].

Cytotoxicity: Stigmasterol, the active constituent of *Cacalia tangutica*, was found to be Cytotoxic to *Spodoptera litura* cells and its action was more marked in comparison to the other active constituents of the plant namely, friedelin and rotenone [51]. Gomez MA stated that stigmasterol in the chloroform extract of *Achillea ageratum* and its cytostatic activity against Hep-2 and McCoy cells was determined. It showed high degree of inhibition when compared with 6-Mercaptopurine against both cultures [52].

Anti-tumor: *Carthami flos* contained stigmasterol which markedly inhibited the tumour promotion in the two-stage carcinogenesis experiments [53]. Also Zhijie G investigated the extracts of *Couepia polyandra* and *Edgeworthia gardneri* revealed the presence of stigmasterol along with other constituents and stigmasterol was found to inhibit the lyase activity of DNA polymerase β and also potentiate the inhibitory effect of the anti-cancer drug bleomycin in cultured A549 cells. These actions were a result of an inhibition of DNA repair synthesis [54].

Hypoglycemic activity and effect on thyroid: Chloroform extract of *Parkia speciosa* was orally administered to the alloxan- induced diabetic rats and it was found to produce a significant depression in blood glucose levels. Structure elucidation of the hypoglycaemic fractions showed the presence of stigmasterol along with β-sitosterol. When these constituents were tested individually they showed no activity which concluded that synergism between these two is necessary to produce the effect [55]. Further, Panda S investigated that, stigmasterol isolated from the bark of *Butea monosperma* revealed

that administration of stigmasterol to mice for 20 days reduced serum triiodothyronine (T_3), thyroxin (T_4), glucose concentration and the activity of hepatic glucose-6-phosphate with a significant increase in insulin indicating its thyroid inhibiting and hypoglycaemic property [56].

Antioxidant: Stigmasterol present in bark of *Butea monosperma* showed decrease in hepatic lipid peroxidation and increase in the activities of catalase, superoxide dismutase and glutathione thereby suggesting its antioxidant property [56].

Antimutagenic activity: Thorns of *Gleditsia sinensis* was investigated for their active constituents and their antimutagenic activity. One terpenoid and four steroids were isolated from the plant out of which stigmasterol was the most active antimutagen showing 51.2% and 64.2% reduction of the induction factor against the mutagen MNNG and NQO respectively, in the SOS chromo test [57].

Anti-inflammatory activity: Acetone extract of *Sideritis foetens* was found to contain sterol fractions composed of stigmasterol, β-sitosterol and campesterol. These fractions were evaluated for their anti-inflammatory activity and they were found to reduce carrageenan induced paw oedema and also inhibited ear oedema induced by 12-O-tetradecanoylphorbol acetate (TPA) after topical application [58]. Also, stigmasterol isolated from *Eryngium foetidum* (Apiaceae) was evaluated by Garcia MD, focussing on auricular oedema induced by 12-O-tetradecanoylphorbol acetate (TPA), by single and multiple application of phlogistic agent and was found to reduce oedema. It also exerts a significant topical anti-inflammatory action [59].

CNS activities: The petroleum ether extract of aerial parts of *Celesia coromandeliane* on preparative TLC gave a fraction which upon IR study revealed that the compound has structural similarity with stigmasterol derivatives and this showed significant analgesic activity as it significantly reduced the number of writhes and stretches induced in mice by 1.2% acetic acid solution. Pretreatment with these fractions caused substantial protection against strychnine- and leptazol- induced convulsions [60]. Likewise, leaf extract of *Perilla frutescens* showed sedative activity as a result of combined effect of stigmasterol and perillaldehyde. Other combinations of the components did not show the same results [61].

CONCLUSION: From the above information it is clear that stigmasterol and its derivatives are of utmost importance and is therefore imperative to further investigate these compounds. Out of numerous valuable constituents found, stigmasterol is one of the potential one and has been isolated from many plants till date and evaluated for many pharmacological and biological activities. It is jussive that more pharmacological studies should be conducted to evaluate the unexploited potential of this constituent.

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