Trop J Nat Prod Res, January 2023; 7(1):2325-2336 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Ferruginol and Sugiol: A Short Review of their Chemistry, Sources, Contents, Pharmacological Properties and Patents

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ARTICLE INFO

Article history:
Received 05 January 2023
Revised 09 January 2023
Accepted 15 January 2023
Published online 01 March 2023

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ABSTRACT

In this short article, the chemistry, sources, contents, pharmacological properties and patents of ferruginol (FG) and sugiol (SG) are reviewed for the first time. Sources of information cited on these two abietane diterpenes were from databases such as Google, Google Scholar, PubMed, Science Direct, J-Stage, Web of Science and PubChem. In the selection of articles, recent references were accorded higher priority apart from their relevance to the topics. Both FG and SG are characterized by a tricyclic ring system with a hydroxyl group and an isopropyl group at ring C. SG has a carbonyl group at ring B that is absent in FG. Found in the bark and root of plant species particularly those belonging to the families Cupressaceae and Lamiaceae, FG and SG have attracted much attention because of their diverse pharmacological properties, notably, their anti-cancer and anti-protozoal activities. Three patents on FG and one on SG are described. Some areas of research requiring further investigations are suggested.

Keywords: Cupressaceae, Lamiaceae, Tricyclic Abietane Diterpenes, Anti-Cancer .

Introduction

Diterpenes are a diverse class of 20-carbon compounds formed by condensation of four isoprene units.[1] They are classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic or macrocyclic diterpenes, depending on their core structures. Among the tricyclic diterpenes are the abietane diterpenes or abietanes that are characterized by three fused six-membered rings and alkyl functional groups at carbons 4, 10 and 13.[2] Some examples of abietanes are ferruginol, sugiol and hinokiol. Diterpenes notably abietane diterpenes including their synthetic derivatives have generated much research interest because of their diverse biological activities and pharmacological properties.[2,3] They include antimicrobial, anti-leishmanial, anti-plasmodial, antifungal, anti-cancer, cytotoxic, antiviral, antiulcer, gastroprotective, cardiovascular, antioxidant as well as anti-inflammatory properties. Recently, the anti-cancer properties of abietane diterpenes from rosemary (carnosic acid, carnosol and rosmanol) have been reviewed.[4] In this short article, the chemistry, sources, contents and pharmacological properties of ferruginol and sugiol (abietane diterpenes) are reviewed for the first time. Some topics of research that warrant further studies are suggested.

Chemistry

Ferruginol

Ferruginol (FG) or abieta-8,11,13-trien-12-ol is a tricyclic abietane diterpene with a molecular formula of $C_{20}H_{30}O$ and molecular weight of 286.5 g/mol.[2,5] Characterized by a tricyclic ring system, FG has a hydroxyl (−OH) group at C12 and an isopropyl [$-CH(CH_3)_2$] group at C13 of ring C (Figure 1).

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Citation: Chan EWC, Wong SK, Chan HT. Ferruginol and Sugiol: A Short Review of their Chemistry, Sources, Contents, Pharmacological Properties and Patents. Trop J Nat Prod Res. 2023; 7(1):2325-2336 http://.www.doi.org/10.26538/tjnpr/v7i2.4

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Its chemical structure is similar to that of hinokiol, except that hinokiol has an −OH group at C3, that is absent in FG.

Sugiol

Sugiol (SG) or 12-hydroxyabieta-8,11,13-trien-7-one is another tricyclic abietane diterpene with a molecular formula of $C_{20}H_{28}O_2$ and molecular weight of 300.4 g/mole.[2,5] SG, like FG, has a −OH group at C12 and a $-CH(CH_3)_2$ group at C13 of ring C (Figure 1). In addition, SG has a carbonyl group at C7 of ring B, that is absent in FG. A carbonyl group is a functional group comprising of a carbon atom that is double-bonded to an oxygen atom (C=O). The carbonyl group is trigonal planar in shape and improves hydrophilicity. In sugiol, the carbonyl group is likely to contribute to the bioactivity of the compound.

Sources and Contents

Ferruginol

FG was first isolated by Brandt and Neubauer in 1939 from the resin of *Podocarpus ferrugineus* (Miro), an endemic tree to New Zealand.[2,3] This abietane diterpene has been reported in different plant parts of 31 species mainly belonging to the families of Cupressaceae (14 species), Lamiaceae (6 species), and Podocarpaceae (4 species) (Table 1). Minor families are Taxaceae, Meliaceae, Martyniaceae, Pedaliaceae and Lauraceae. FG is most often isolated from the bark (10) and root (9) of species.

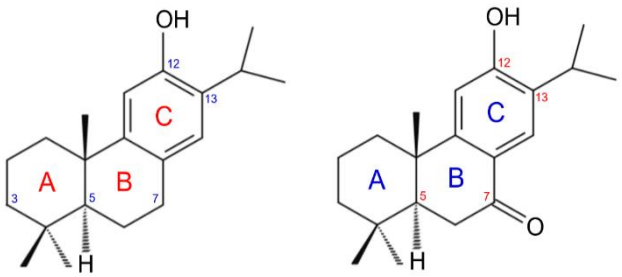

Figure 1. Chemical structures of ferruginol (left) and sugiol (right).

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Table 1: Plant sources of ferruginol and sugiol.

No.	Compound & species	Family	Plant part	Reference
	Ferruginol			
1	*Amentotaxus formosana*	Taxaceae	Bark	9
2	*Azadirachta indica*	Meliaceae	Root	10
3	*Calocedrus* var. *formosa*	Cupressaceae	Bark	11
4	*Caryopteris mongholica*	Lamiaceae	Aerial part	12
5	*Chamaecyparis obtusa*	Cupressaceae	Heartwood	13
6	*Craniolaria annua*	Martyniaceae	Root	14
7	*Cryptomeria japonica*	Cupressaceae	Leaf & bark	15
			Heartwood	16-18
			Bark	19
			Leaf	20
8	*Cupressus arizonica*	Cupressaceae	Fruit & branchlet	7
9	*Cupressus sempevirens*	Cupressaceae	Fruit	21
10	*Harpagophytum procumbens*	Pedaliaceae	Root	22
11	*Juniperus excelsa*	Cupressaceae	Aerial part	23
			Fruit	24
12	*Juniperus phoenicea*	Cupressaceae	Fruit	24
13	*Juniperus procera*	Cupressaceae	Aerial part	25
			Fruit	24
			Root	6
			Leaf	6
			Seed	6,26
14	*Papuacerdus papuana*	Cupressaceae	Leaf	27
15	*Persea nubigena*	Lauraceae	Wood	28
16	*Podocarpus andina*	Podocarpaceae	Stem bark	28
17	*Podocarpus ferrugineus*	Podocarpaceae	Bark	29
18	*Podocarpus nubigenus*	Podocarpaceae	Wood	30,31
19	*Prumnopitys andina*	Podocarpaceae	Bark	32
			Stem bark	30,31,33
			Bark & wood	34,35
20	*Salacia oblonga*	Celastraceae	Leaf & root	36
21	*Salvia hypargeia*	Lamiaceae	Root	37
22	*Salvia lachnocalyx*	Lamiaceae	Root	38
23	*Salvia miltiorrhiza*	Lamiaceae	Root	39,40
			Cell culture	41,42
24	*Salvia sahendica*	Lamiaceae	Root	43
25	*Salvia staminea*	Lamiaceae	Aerial part	44
26	*Sequoia sempervirens*	Cupressaceae	Cone	45
27	*Taiwania cryptomerioides*	Cupressaceae	Heartwood	46
28	*Tetraclinis articulata*	Cupressaceae	Resin	47
29	*Thuja plicata*	Cupressaceae	Aerial part	48
31	*Thuja standishii*	Cupressaceae	Stem bark	49,50
31	*Torreya nucifera*	Taxaceae	Leaf	51
	Sugiol			
1	*Austrocedrus chilensis*	Cupressaceae	Bark	32

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2	*Calocedrus formosana*	Cupressaceae	Bark	52, 53
3	*Chamaecyparis obtusa*	Cupressaceae	Heartwood	13
4	*Cephalotaxus lanceolata*	Taxaceae	Leaf & twig	54
5	*Cladonia rangiferina*	Cladoniaceae	Aerial part	55
6	*Clerodendrum cyrtophyllum*	Lamiaceae	Stem	56
7	*Cryptomeria japonica*	Cupressaceae	Leaf & bark	15
			Bark	8,19
			Heartwood	57
8	*Cunninghamia konishii*	Cupressaceae	Wood	58
9	*Juniperus chinensis*	Cupressaceae	Bark	59
10	*Juniperus polycarpus*	Cupressaceae	Fruit	60
11	*Juniperus procera*	Cupressaceae	Aerial part	25
			Fruit	24
12	*Metasequoia glyptostroboides*	Cupressaceae	Cone	61-63
13	*Peltodon longipes*	Lamiaceae	Root	40,64
14	*Plectranthus barbatus*	Lamiaceae	Aerial part	65
15	*Podocarpus ferrugineus*	Podocarpaceae	Bark	29
16	*Salvia albocaerulea*	Lamiaceae	Leaf	66
17	*Salvia bowleyana*	Lamiaceae	Root	67
18	*Salvia hypargeia*	Lamiaceae	Root	37
19	*Salvia miltiorrhiza*	Lamiaceae	Root	68
20	*Salvia staminea*	Lamiaceae	Aerial part	44
21	*Sequoia sempervirens*	Cupressaceae	Cone	45,69,70
22	*Taiwania cryptomerioides*	Cupressaceae	Heartwood	46
23	*Taxodium distichum*	Cupressaceae	Bark	71
24	*Tetraclinis articulata*	Cupressaceae	Resin	47
25	*Thuja plicata*	Cupressaceae	Aerial part	48
26	*Thuja standishii*	Cupressaceae	Stem bark	50

The content of FG has been quantified in *Juniperus procera* (Cupressaceae), where the root extract contained a higher amount (4.4 µg/g), followed by the leaf (0.43 µg/g) and seed (0.42 µg/g).[6] In the branchlet and leaf of *Cupressus arizonica*, the content of FG (in relative area percent) has been reported to be 10.4% and 5.9%, respectively.[7] FG (76.6% of the total content of compounds in exudates) was the most abundant compound in the bark of *Cryptomeria japonica*.[8]

Sugiol

SG has been reported in 26 species mainly of the families Cupressaceae (15 species) and Lamiaceae (8 species) (Table 1). Minor families are Taxaceae, Cladoniaceae and Podocarpaceae. SG is most often isolated from the bark (8) and root (4) of species.

Pharmacological Properties

Ferruginol

Pharmacological properties of FG included anti-cancer, anti-protozoal, antiviral, antioxidant, gastroprotective, neuroprotective, cardioprotective, antibacterial, anti-inflammatory, ulcerative (UC) inhibitory, cholesterol inhibitory, cholinesterase (ChE) inhibitory, Epstein-Barr virus early antigen (EBV-EA) inhibitory, immunological and enzyme inhibitory activities (Table 2).

Cancer cells susceptible to FG include gastric, prostate, lung, cervical, breast and colon cancer cells, together with leukemia and melanoma cells (Table 2). Interestingly, two articles on the anti-cancer properties of FG were retracted.[74,75] An editorial decision was made to retract an earlier article on the anti-cancer effects of FG on MDA-T32 thyroid cancer cells.[75] in March 2021 due to breach of publishing guidelines, following the identification of non-original and manipulated figures. Almost concurrently, due to anomalies pointed out by an interested reader that were later verified by the Editor, an editorial decision was made to retract the article on the anti-cancer effects of FG on OVCAR-3 human ovary cancer cells[74] in February 2021.

Sugiol

The biological and pharmacological significance and mechanisms of SG have been reviewed.[87] Properties reviewed included anti-cancer, antioxidant, anti-inflammatory, antimicrobial, antiviral and cardiovascular activities. In Table 3, pharmacological properties of SG included anti-cancer, anti-protozoal, enzyme inhibitory, antibacterial, anti-inflammatory, anti-fungal, α-glucosidase inhibitory, anti-tyrosinase, hepatoprotective and antioxidant activities. Cancer cells susceptible to SG include prostate, pancreatic, ovarian, lung and endometrial cancer cells, together with melanoma cells. Pancreatic cancer cells appear to be particular susceptible to SG.[40,71,88]

Other Studies

There are no *in vivo* studies on the pharmacological properties of FG and SG, unlike corosolic acid from *Lagerstroemia speciosa* where its anti-diabetic effects are well-studied using diabetic mice.[95] Another observation is the lack of studies on structure-activity relationships (SAR) of FG and SG, unlike acacetin and chrysoeriol where their SAR on antioxidant, cytotoxicity towards cancer cells and enzyme inhibitory activities have been reported.[96]

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Table 2: Pharmacological properties of ferruginol (FG).

Bioactivity	Effect and mechanism involved	Reference
Anti-cancer	FG exhibited cytotoxic effects on A549 and CLI-5 lung cancer cells by inducing apoptosis *via* a caspase-dependent mitochondrial apoptotic pathway. In CLI-5 xenograft mice, FG significantly suppressed the growth of subcutaneous tumors.	20
	FG induced apoptosis in PC3 prostate cancer cells by activating caspases and AIF, and inhibiting Ras/PI3K and STAT3/5 proteins.	28
	FG inhibited the growth of AGS gastric cancer cells with IC_{50} value of 27 µM.	31
	FG weakly inhibited the growth of SW620 colon, MDA-MB-231 breast, HCT116 colon, NCI-H23 lung and A549 lung cancer cells (GI_{50} < 50 µg/mL).	45
	FG inhibited A549 lung cancer cells (GI_{50} = 31 µM), but not HBL-100 breast, T-47D breast, HeLa cervical, SW1573 lung and WiDr colon cancer cells.	47
	Retracted: FG exhibited anticancer effects in OVCAR-3 ovary cancer cells by inducing apoptosis, inhibiting cancer cell migration, and inducing G2/M cell cycle arrest.	72
	Retracted: FG inhibited the growth of MDA-T32 thyroid cancer cells (IC_{50} = 12 µM) by inducing apoptosis, endogenous ROS production, mitochondrial membrane potential loss, and suppression of MAPK and PI3K/AKT signaling pathways.	73
	FG inhibited HeLa cervical cancer, and Jurkat and U937 leukemia cells with IC_{50} values of 65, 48 and 21 µM, respectively. Against Vero normal cells, cytotoxicity was very weak (IC_{50} = 90 µM).	74
	FG inhibited the growth of SK-Mel-28 melanoma cells with IC_{50} values of 85 µM at 24 h and 55 µM at 48 h. Induction of apoptosis involved inhibition of caspase-3 activity, p38 phosphorylation and translocation of NF-κB.	75
	FG inhibited MCF-7 breast cancer cells with IC_{50} value of 12 µM by inducing apoptosis, and by modulating the expression of inflammatory proteins such as TNF-α, IL-6, NF-κB, iNOS and COX-2, and apoptotic proteins such as caspases-3 and -9.	76
	FG inhibited the growth of HCT‑116 colon cancer cells by inducing apoptosis *via* the mitochondrial‑mediated apoptotic pathway, along with the suppression of Bcl‑2, and improvement in caspases‑3 and -9, cytochrome‑c, and Bax expressions.	77
Anti-protozoal	FG displayed cytotoxic effects against trypomastigotes (IC_{50} = 52 µM) and epimastigotes (IC_{50} = 90 µM) of *Trypanosoma cruzi* and against fibroblastic Vero cells (IC_{50} = 51 µM).	14
	FG displayed significant *in vitro* anti-plasmodial activity against chloroquine-resistant (K1) and chloroquine-sensitive (D10) strains of *Plasmodium falciparum* with IC_{50} values of 0.95 and 0.63 µg/mL, respectively. Against CHO and HepG2 cells, cytotoxicity was very weak (IC_{50} = 52 and 44 µg/mL), respectively.	22

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	FG displayed anti-malarial activity against D6 chloroquine-sensitive and W2 chloroquine-resistant strains of *P. falciparum*, with IC_{50} values of 4.2 and 3.5 µg/mL, respectively.	24
	FG displayed anti-leishmanial activity against *Leishmania donovani* with IC_{50} value of 3.5 µg/mL.	24
	FG inhibited K1 strain of *P. falciparum* and STIB 900 strain of *Trypanosoma brucei rhodesiense*. Anti-plasmodial activity (IC_{50} = 0.9 µM) was much stronger than anti-trypanosomal activity (IC_{50} = 12.8 µM).	43
	FG displayed anti-leishmanial activity by inhibiting *L. donovani* (IC_{50} = 12 µM), but not *L. infantum*, *L. guyanensis* and *L. amazonensis*.	47
	FG inhibited 3D7 chloroquine-sensitive and K1 chloroquine-resistant *P. falciparum* with EC_{50} values of 2.5 and 1.3 µg/mL, and selective index of 4.6 and 8.6, respectively.	47,78
Antiviral	FG inhibited the replication of SARS-CoV $3CL^{pro}$ (93%) with IC_{50} value of 49.6 µM. FG was the most potent among eight diterpenes tested.	51
	FG inhibited the replication of SARS-CoV with EC_{50} value of 1.39 µM. FG was the most potent among five diterpenes tested.	54
	Two FG analogues, but not FG, inhibited HHV-1, HHV-2 and DENV-2.	74
	FG analogues, but not FG, showed anti-Zika virus activity with EC_{50} values ranging from 0.67 to 18.6 µM.	79
	FG (12.5 µg/mL) displayed antiviral activity against ZIKV and DENV-2 with 38% and 28% inhibition, respectively. There was no activity against HHV-1.	80
Antioxidant	FG displayed promising free radical scavenging ability, comparable to that of BHT, and possessed significantly better electron-donating activity than sugiol.	5
	FG exhibited stronger activity than carnosic acid and α-tocopherol for linoleic acid oxidation. Ferruginol had the lowest antioxidant activity for DPPH radical scavenging compared to carnosic acid, α-tocopherol and BHT.	81
Gastroprotective	FG exerted gastroprotective effects on AGS and MRC-5 cells by increasing PG content, protecting from lipid peroxidation, and improving gastric ulcer healing. FG inhibited gastric lesions and displayed significant ulcer healing activity in rats.	34
	FG acted as a gastroprotective agent in rats and mice with ethanol-induced gastric lesions by increasing gastric PG content, reducing gastric acid output, improving antioxidant capacity of the gastric mucosa and maintaining the gastric GSH level.	82
Neuroprotective	FG protected against Aβ oligomers-induced neurodegenerative alterations. Aβ oligomers are recognized as early neurotoxic intermediates with a key role in the synaptic dysfunction of AD.	33
	FG prevented the degeneration of dopaminergic neurons by promoting the clearance of α-synuclein, relevant to the treatment of PD and other neurodegenerative diseases.	83

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Cardioprotective	FG protected against ISO-induced MI in rats by reducing pro-inflammatory mediators, heart weight, cardiac damaged biomarkers, and lipid peroxidation.	84
	FG displayed cardioprotective effects in mice with DOX-induced cardiotoxicity by restoring MB and FAO *via* the SIRT1–PGC-1α pathway.	85
Antibacterial	FG inhibited *Enterococcus faecalis*, *Staphylococcus aureus*, *S. epidermidis*, and MRSA with MIC values ranging from 6.3 to 12.5 mg/mL.	19
Anti-inflammatory	FG exhibited significant anti-inflammatory activity by inhibiting nitrite production in RAW 264.7 cells with IC_{50} value of 28.6 µM.	9
	FG showed topical anti-inflammatory activity *in vivo* models of mice with AA (21.0%) and or TPA (20.5%).	35
UC inhibitory	FG efficiently inhibited DSS-induced UC in mice by ameliorating severe inflammation *via* inhibition of COX-2, MMP-9, and NF-κB signaling.	86
Cholesterol inhibitory	FG displayed significant inhibitory activity on cholesterol absorption (62.5% inhibition at 20 µg/mL) in mice RAW 264.7 cells, with IC_{50} value of 9.5 µg/mL.	11
ChE inhibitory	FG inhibited AChE (75%) and BChE (88%).	44
EBV-EA inhibitory	FG exerted 100% inhibitory effect on EBV-EA induced by TPA in Raji cells.	50
Immunological	FG induced the formation of IL-10-producing regulatory T cells by modulating the function of DC that are specialized antigen-presenting cells initiating immunity on encountering antigens associated with infection and inflammation.	17
Enzyme inhibitory	FG inhibited butyrylcholinesterase (99%) and elastase (65%).	37

Abbreviations: AA = arachidonic acid, AChE = acetyl cholinesterase, AD = Alzheimer's disease, AGS = gastric adenocarcinoma, AIF = apoptosis-inducing factor, BChE = butyryl cholinesterase, BHT = butylated hydroxytoluene, CAT = cholesterol acyltransferase, ChE = cholinesterase, COX-2 = cyclooxygenase-2, DC = dendritic cells, DENV-2 = dengue virus type 2, DOX = doxorubicin, DPPH = 2,2-diphenyl-1-picrylhydrazyl, DSS = dextran sulfate sodium, EBV-EA = Epstein-Barr virus early antigen, FAO = fatty acid oxidation, GSH = glutathione, GPase = glycogen phosphorylase, HHV-1 and HHV-2 = human herpes virus types 1 and 2, IL = interleukin, iNOS = inducible nitric oxide synthase, ISO = isoprenaline hydrochloride, MAPK = mitogen-activated protein kinase, MB = mitochondrial biogenesis, MI = myocardial infarction, MIC = minimum inhibitory concentration, MMP-9 = matrix metalloproteinases-9, MRSA = methicillin-resistant *Staphylococcus aureus*, NF-*κ*B = nuclear factor kappa B, PD = Parkinson's disease, PG = prostaglandin, PGC-1α = peroxisome proliferator-activated receptor gamma coactivator-1, PI3K = phosphatidylinositol-3-kinase, ROS = reactive oxygen species, SARS-CoV = severe acute respiratory syndrome associated coronavirus, SIRT1 = sirtuin 1, STAT3/5 = signal transducer and activator of transcription 3/5, TNF-α = tumor necrosis factor-alpha, TPA = 12-*O*-tetradecanoylphorbol 13-acetate, UC = ulcerative colitis, and ZIKV = Zika virus.

Patents

Ferruginol

A patent on FG was filed by N. Inoue, H. Ohinata, T. Matsuzaki, Y. Yonei, K. Kitagawa & F. Harada as inventors, with Shokuhin Sangyo Co. Ltd. in Tokyo, Japan, as the assignee.[97] The Japanese patent JPH05294878A was dated November 1993 and entitled, 'Purification of ferruginol.' This invention enables the high-efficient purification of FG without using organic solvent that is undesirable in the food product industry. FG from the bark of *C. japonica* or a crude extract is purified using high-pressure supercritical carbon dioxide. Purified FG obtained is useful as an antimicrobial or antioxidant agent for food and pharmaceutical products.

Another patent on FG was filed by A. Evans David & U.Y. Nguyen as inventors, with Norac Technologies Inc. in New Zealand as the assignee.[98] The New Zealand patent NZ261825(A) was dated April 1996 and entitled, 'Cosmetic composition comprising a phenolic diterpene of the ferruginol type.' The invention entails a skin care composition containing an effective amount of a phenolic diterpene compound of the FG type. The compound can be dissolved, dispersed or encapsulated in cosmetic solutions, lotions, creams and liposomes to provide skin care products. Such a composition is effective against the

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production of peroxides in the skin, resulting from sunlight, heat, radiation and the aging process.

A third patent on FG was filed by M.A. Gonzalez Cardenete & L.A. Betancur Galvis as inventors, with University of Antioquia and University of Valencia in Spain as assignees.[99] The Spanish patent ES2586505B1 was dated July 2017 and entitled, 'Ferruginol analogues as antiviral agents.' The invention relates to antiviral compounds derived from abietane diterpenes, specifically ferruginol analogues, for use against dengue virus serotypes (DENV1-4), and human herpes viruses type 1 (HHV-1) and type 2 (HHV-2).

Sugiol

A patent on SG was filed by T. Hattori, T. Katagiri, A. Kanamaru & T. Kato as inventors, and Pola Chemical Industries Inc. in Japan as the assignee.[100] The Japanese patent JPH11139931A was dated May 1999 and entitled, 'Preparation for external use for skin whitening.' The invention entails a method for preparation of a topical formulation for use as skin whitening and/or preventing/ameliorating skin pigmentation, after exposure to the sun. This formulation contains an effective amount of SG.

Table 3: Pharmacological properties of sugiol (SG).

Bioactivity	Effect and mechanism involved	Reference
Anti-cancer	SG weakly inhibited the growth of SW620 colon, MDA-MB-231 breast, HCT116 colon, NCI-H23 lung, and A549 lung cancer cells (GI_{50} < 50 µg/mL).	45
	SG inhibited the growth of DU145 prostate cancer cells *via* inactivation of JAK2/ STAT3 pathway	69
	SG inhibited MIA PaCa-2 pancreatic cancer cells and MV-3 melanoma cells with IC_{50} values of 17.9 and 34.1 µM, respectively.	40
	SG moderately inhibited A549 lung cancer cells (GI_{50} = 80 µM), but not HBL-100 breast, T-47D breast, HeLa cervical, SW1573 lung and WiDr colon cancer cells.	47
	SG inhibited DU145 prostate cancer cells by suppressing STAT3 activity *via* the regulation of transketolase and ROS-mediated ERK activation.	70
	SG was cytotoxic to MIA PaCa-2 pancreatic cancer cells (IC_{50} = 15 µM), and inhibited their growth by inducing apoptosis, G2/M cell cycle arrest, and ROS production, and by inhibiting cell migration.	88
	SG strongly inhibited PANC-1 pancreatic cancer cells (cultured under glucose-starved conditions) with EC_{50} value of 9.0 µM. Against NHDF cells, cytotoxicity of SG was very weak with EC_{50} value of 68 µM.	71
	SG inhibited SKOV3 ovarian cancer cells with IC_{50} value of 25 µM. Mechanisms included apoptosis, cell cycle arrest, and blocking of the RAF/MEK /ERK signaling pathway.	89
	SG suppressed the growth, migration, and invasion of human endometrial cancer cells *via* the induction of apoptosis and autophagy. Against HEC-1-A, HEC-1-B and KLE, the IC_{50} values of SG were 14, 14 and 16 µM, respectively.	90
Anti-protozoal	SG exhibited antimalarial activity against D6 and W2 strains of *P. falciparum* with IC_{50} values of 472 and 409 ng/mL, respectively.	60
	SG displayed antimalarial activity against D6 chloroquine-sensitive strain (IC_{50} value of 3.0 µg/mL) but not W2 chloroquine-resistant strain of *P. falciparum*.	24
	SG displayed inhibitory activity against *Leishmania infantum* promastigotes and amastigotes at 48 h with IC_{50} values of 5.5 and 5.7 µg/mL, respectively.	91

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	SG did not display inhibitory activity against all four *Leishmania* species tested, namely, *L. donovani*, *L. infantum*, *L. guyanensis* and *L. amazonensis*.	47
Enzyme inhibitory	SG strongly inhibited XO activity with IC_{50} value of 6.8 µM.	92
	SG inhibited GPase with IC_{50} value of 12.7 µM.	21
	SG inhibited topo I with IC_{50} value of 2.8 µM.	64
	SG exerted 100% inhibitory effect on EBV-EA induced by TPA in Raji cells.	50
Antibacterial	SG possessed antibacterial activity with MIC values of 40 and 50 µg/mL against *Bacillus subtilis* and *S. aureus*, respectively.	66
	SG possessed antibacterial activity against MRSA with diameter of inhibition zone of 20 mm at 100 mg/disc. No activity was observed against VRE.	55
	SG displayed antibacterial activity against food-borne pathogens with diameters of inhibition zone of 10−16 mm at 50 µg/disc.	62
Anti-inflammatory	SG inhibited LPS-induced TNF-α and IL-1β expression as well as ROS and MAPKs activation in macrophages.	52
	SG significantly inhibited COX-2 activity with IC_{50} value of 5 µg/mL.	58
Anti-fungal	Sugiol at 100 µg/disc displayed anti-fungal effect against *Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. guilliermondii* at diameters of zone of inhibition ranging from 8−13 mm.	63
α-Glucosidase inhibitory	SG inhibited α-glucosidase at values ranging from 12.3−63.5%, suggesting its anti-diabetic potential.	93
Anti-tyrosinase	SG inhibited tyrosinase at values ranging from 28.2−67.4%, suggesting its anti-melanogenesis potential.	93
Hepatoprotective	SG was effective in reducing elevated liver enzymes as indication of hepatoprotection. The reduction of SGOT, SGPT, ALP and TB was 32.6%, 60.3%, 37.4% and 36.8%, respectively.	25
Antioxidant	SG significantly scavenged DPPH, nitric oxide, superoxide and hydroxyl free radicals by 79%, 72%, 73% and 85%.	94

Abbreviations: A-G = alpha-glucosidase, ALP = alkaline phosphatase, AR = aldose reductase, COX-2 = cyclooxygenase-2, DPPH = 2,2-diphenyl-1-picrylhydrazyl, EBV-EA = Epstein-Barr virus early antigen, ERK = extracellular signal-regulated protein kinase, GPase = glycogen phosphorylase, IL = interleukin, JAK2 = Janus kinase 2, LPS = lipopolysaccharide, MAPKs = mitogen-activated protein kinases, MEK = MAPK/ERK kinase, MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, NHDF = normal human dermal fibroblast, RAF = rapidly accelerated fibrosarcoma, ROS = reactive oxygen species, SGOT = serum glutamate oxaloacetate transaminase, SGPT = serum glutamate pyruvate transaminase, STAT3 = signal transducer and activator of transcription 3, TB = total bilirubin, TNF = tumor necrosis factor, Topo I = topoisomerase I, TPA = 12-*O*-tetradecanoylphorbol 13-acetate, VRE = vancomycin-resistant *Enterococci*, and XO = xanthine oxidase.

Conclusion

This article presents an overview of the chemical structures, sources, contents, pharmacological properties and patents of FG and SG isolated from nature. They are tricyclic abietane diterpenes that are commonly isolated from plant species of the families Cupressaceae and Lamiaceae. Currently, FG and SG are not commercially available and studies on these two compounds would require their isolation from plant species

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such as *C. japonica* and *J. procera*. Lacking are *in vivo* studies on the pharmacological properties using animal models, structure-activity relationships, clinical trials and safety evaluation of FG and SG. Their chemopreventive efficacy when used alone or in combination with other chemotherapy agents, their ability to reverse multi-drug resistance in cancer cells, and their structural modifications to synthesis novel derivatives or analogues with enhanced anti-cancer properties are worth exploring. Finally, bioavailability, pharmacokinetics, biotransformation, dose-response, synergism and side-effects of FG and SG are warranted.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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