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Review

Anti-inflammatory activity of natural coumarin compounds from plants of the Indo-Gangetic plain

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Abstract: Natural compounds are a repertoire of organoleptic molecules. This indicates that although they are not a significant source of nutrients, still they exhibit a wide range of medicinal properties through their plethora of anti-inflammatory and immune-modulatory activities. Coumarins, found in a variety of plants from different biodiversity regions, also have been reported to be present in many plants of the Indo-Gangetic plain. Here, we would attempt to enumerate the natural coumarin compounds, their pharmaco-therapeutic potential and their occurrence as well as abundance in the flora of the aforesaid biodiversity region. Coumarins, derived their name from the French word "coumarou" for Tonka bean. First isolated in 1820, coumarin still finds its relevance in the study of implementation of natural compounds in treating neuro-degenerative and cancer-like fatal diseases. Naturally occurring benzopyrones, chemically classified as lactones and coumarin compounds need to be reviewed to develop new era drugs from natural resources. This promises an effective treatment regimen with minimal side effects and also paves the path for a sustainable future with efforts to manage our health problems from the plant products in our immediate environment.

Keywords: coumarin; natural compound; Indo-Gangetic plain; pharmaco-therapy; lactones

1. Introduction

Coumarin nucleus is present in several plants. Studies have revealed that various phytoconstituents have been derived from coumarin nucleus that has pronounced anti-inflammatory activities. Certain coumarins-derived phytocompounds like columbiatnetin,visniadin, marmin, umbelliferon, scopoletin etc., have been reported to have potential anti-inflammatory activities. These compounds have also been reported to have potent antioxidant and radical scavenging potential which may complement their anti-inflammatory activities [1]. Coumarin derivatives which get synthesized naturally in various plants and also the compounds derived from coumarin and synthesized in laboratories, both are reported to have excellent anti-inflammatory effects. There have been several studies evaluating the anti-inflammatory and other pharmacological potential of natural and synthetic coumarin derivatives with the interest of developing useful and potent drugs for combating various pain and inflammatory conditions in animal bodies [2]. Studies show that the biological *in vitro* anti-inflammatory activities of coumarin derivatives are concentration-dependent [3].

Inflammation is an essential, immuno-protective physiological response to any kind of irritant or aggression [4]. The reaction of inflammation may be localized or may be generalised depending on the intensity of the stimulus exposed to. Inflammation can get triggered by various factors. Some of these include injury, trauma, exposure to toxins, pathogen attack etc., [5]. Several immune cells act together when our body encounters any kind of inflammation. In the process, various different types of chemicals are released which include substances like histamine and bradykinin. Together those substances are called as inflammatory mediators. They all act together with a goal of removing the cause of inflammation and promoting a healing process. Thus, in a nutshell, inflammation is a protective mechanism of our body and is inevitable to maintain a good health [6]. Besides, other events that occur during inflammation are alteration in vascular permeability and leukocyte recruitment and accumulation [7]. These cause dilatation of the blood vessels which in turn facilitates movement and accumulation of more and more leukocytes at the site of inflammation. Leukocyte chemotaxis occurs from circulation to the site of inflammation [8]. Leukocytes fight back the infection and devour the pathogens to reduce the cause of inflammation and thus help to mitigate the condition of inflammation. Also, leukocytes release inflammatory mediators at the site of inflammation which causes further inflammatory responses [7]. Dilation of blood vessels causes swelling of the site of inflammation. The inflammatory mediators irritate the nerve endings at the site of inflammation and send a pain signal to our central nervous system making us aware of the occurrence of inflammation at a particular site in our body and thus we tend to take care of the inflamed site. The prime inflammatory mediators other than histamine and bradykinin are neuropeptides, cytokines, growth factors and neurotransmitters. Any kind of pain is reported to be having an origin of inflammation or inflammatory response [9].

Studies conducted for several years reveal that coumarins and its derivatives can mitigate inflammation and inflammatory reactions by effecting different types of receptors like Toll-like receptors (TLR), and by effecting various signalling pathways and molecules which include the inflammasomes, Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), nuclear factor- κ-light-chain-enhancer of activated B cells (NF- κB) and transforming growth factor-β/small mothers against decapentaplegic (TGF-β/SMAD) pathways etc. [10]. Studies conducted using six different coumarins derivatives of plant source showed that they have potent anti-inflammatory effects against intestinal inflammation. The study further reveals that the anti-inflammatory activities of these six coumarin derivatives, namely

scopoletin, scoparone, fraxetin, 4-methyl-umbelliferone, esculin and daphnetin had a correlation to their antioxidant properties [11]. Certain coumarins derived from natural plant products like esculetin, fraxetin, daphnetin etc., have been evaluated and are reported as inhibitors of lipoxygenase and cyclooxygenase (COX) enzymes [12]. COX plays an important role in the biosynthesis of prostaglandins H2 from arachidonic_acid (AA). Prostaglandin H2 is a precursor for various molecules like prostaglandins, prostacyclins and thromboxanes which play crucial roles in the pathophysiology of pain and inflammation [13]. The natural coumarin derivatives have also been recognised to have inhibitory effects on neutrophil-dependent superoxide anion generation [12]. These findings show that the natural coumarin derivatives possess both anti-nflmmatory and antioxidant potential thus qualifying as them as excellent candidates for the development of anti-inflammatory drugs.

2. Coumarin compounds rich Indo-gangetic plants

Coumrain compounds have been reported to be present in various plants naturally. These compounds are known to be present in a pretty high concentration in tonka bean i.e., *Coumarouna odorata* (Fabaceae) [14]. Other plants reported to be rich in coumarin compounds are cassia cinnamon and liquorice [15]. Licorice is known as liquorice, kanzoh in Japanese and is known as gancao in Chinese. It is actually the name applied to the roots and stolons of some Glycyrrhiza species (Leguminosae or Fabaceae). The genus Glycyrrhiza consists of almost 30 species [16]. Licorice is known to be used by human since ages. Vanilla grass, *Anthoxanthum odoratum* is also reported to be rich in coumarins compounds [17]. Sweet clover *Melilotus sp.* is also reported to be rich in coumarin compounds [18]. Besides these, *Justicia pectoralis, Ferula L., Pachypleurum Hoff., Prangos Lindl., Heracleum L., Conioselinum Fisch., Libanotis L., Seseli L* etc. were found to be containing various types of coumarins compounds [19]. Cherry blossoms, apricots and strawberries also contain coumarin compounds but in smaller quantities [19]. Studies reveal that more than one thousand and three hundred coumarins have been identified from various plant sources [20].

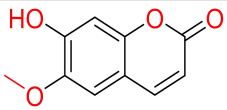
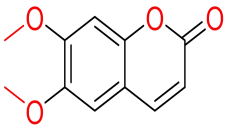
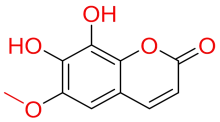
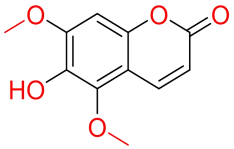
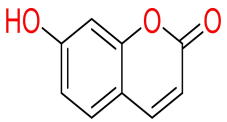
3. Anti-inflammatory activities of Coumarin compounds

Coumarins are natural benzopyrone compounds (2*H*-1-benzopyran-2-one), widely and commonly distributed in many medicinal plants. These are actually fused benzene and α-pyrone rings. These compounds have been reported to have a wide variety of pharmacological potentials which include ani-inflammatory, anti-malarial, anti-viral, anti-fungal, neuro-protective, anti-convulsant, anti-hypertensive, antibacterial, anti-coagulant, anticancer etc. [14] Each of these bio-potential of coumarins have significant pharmacological value. Our aim in this review is to highlight the anti-inflammatory potential of the natural coumarins compounds from the plants of Indo-Gangetic plains.

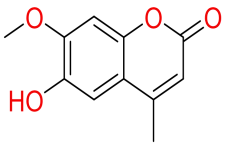
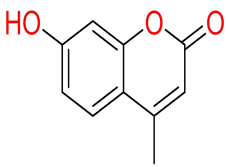
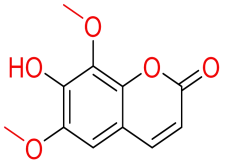
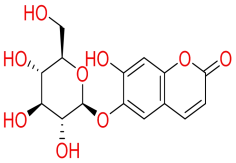
Table 1 represents the list of some potent anti-inflammatory compounds and the plants they have been recognized to be present in. The mechanism of anti-inflammatory of these coumarins compounds isolated from plants of Indo-Gangetic plains are also mentioned in the table in brief.

Besides the plants mentioned in Table 1, cherry blossoms, apricots and strawberries also contain coumarin compounds in smaller quantities [19]. Studies reveal that more than one thousand and three hundred coumarins have been identified from various plant sources [20]. Studies reveal presence of coumarin compounds in plants like *Hypericum perforatum* (Saint John Wort), *Uncaria tomentosa* (Cat's Claw), *Passiflora incarnata* (Passion Flower), *Aesculus hippocastanum* (Horse-chestnut), *Tilia cordata* (Lime Tree), *Lawsonia inermis* (Henna) etc. [21].

Table 1. Coumarin compounds, their source plants and brief mechanism of anti-inflammatory activities.

Sl No.	Coumarin compounds	IUPAC name	Formula	Structure	Plant (common names)	Scientific names	Mode of anti-inflammatory action	References
1	Scopoletin	7-Hydroxy-6-methoxy-2H-1-benzopyran-2-one	$C_{10}H_8O_4$		Datura or Indian thornapple Virgate wormwood Resinous kamala Fenugreek	*Datura metel* *Artemisia scoparia* *Mallotus resinosus* *Trigonella foenum-graecum*	Works by inhibiting the pro-inflammatory cytokines	[22–25]
2	Scoparone	6,7-dimethoxychromen-2-one	$C_{11}H_{10}O_4$		Virgate wormwood Wormwood	*Artemisia scoparia* *Artemisia* absinthium	Works primarily by suppressing the NF-κB signalling inflammatory pathway	[26–29]
3	Fraxetin	7,8-Dihydroxy-6-methoxy-2H-1-benzopyran-2-one	$C_{10}H_8O_5$		Thale cress, mouse-ear cress or arabidopsis Datura or trumpet flower	*Arabidopsis thaliana* *Datura stramonium*	Works by suppressing pro-inflammatory cytokines induced NF-κB signalling inflammatory pathway	[30–33]
4	Fraxinol	6-hydroxy-5,7-dimethoxychromen-2-one	$C_{11}H_{10}O_5$		Prostrate cherry, mountain cherry, Rock Cherry, Creeping Cherry, Spreading Cherry	*Prunus prostrata*	Works by by inhibiting T-cells and prostaglandin biosynthesis	[34–37]
5	Umbelliferone	7-hydroxychromen-2-one	$C_9H_6O_3$		Coriander Toothbrush Tree, Miswak	*Coriandrum sativum* *Salvadora persica*	Works by suppressing and downregulating certain genes involved in inflammatory pathways like the genes of TLR4 and NF-κB	[38–41]

Continued on next page

Sl No.	Coumarin compounds	IUPAC name	Formula	Structure	Plant (common names)	Scientific names	Mode of anti-inflammatory action	References
6	6-hydroxy-7-methoxy-4 methyl coumarin	6-hydroxy-7-methoxy-4-methylchromen-2-one	$C_{11}H_{10}O_4$		Bishop's flower, false bishop's weed, laceflower, bullwort, lady's lace, false Queen Anne's lace	*Ammi majus*	Reported to exhibit anti-inflammatory activity *in vivo* in carrageenan-induced rat paw edema protocol	[42–45]
7	4-methyl-umbelliferone	7-hydroxy-4-methylchromen-2-one	$C_{10}H_8O_3$		Bishop's flower, false bishop's weed, laceflower, bullwort, lady's lace, false Queen Anne's lace	*Ammi majus*	Works by inhibiting the pro-inflammatory cytokines	[46,47]
8	Isofraxidin	7-hydroxy-6,8-dimethoxychromen-2-one	$C_{11}H_{10}O_5$		Celery	*Apium graveolens*	Works by reducing pro-inflmmatory cytokines and by attenuating the increased expression of inflammatory enzymes	[48–51]
9	Esculin	7-hydroxy-6-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-2-one	$C_{15}H_{16}O_9$		Barley	*Hordeum spontaneum*	Reported to work by reducing proinflammatory and inflammatory cytokines	[52–54]

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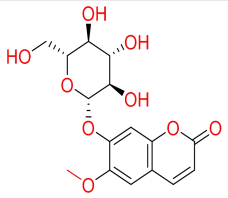
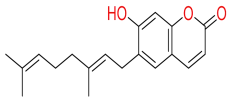
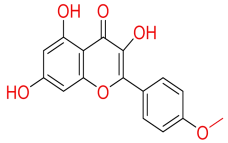
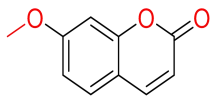
Sl No.	Coumarin compounds	IUPAC name	Formula	Structure	Plant (common names)	Scientific names	Mode of anti-inflammatory action	References
10	Scopolin or Murrayin or Scopoletin 7-glucoside	6-methoxy-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-2-one	$C_{16}H_{18}O_9$		Thale cress, mouse-ear cress or arabidopsis Mugwort, wormwood, Orange berry and gin berry Orange jasmine, orange jessamine, china box or mock orange	*Arabidopsis thaliana* *Artemisia minor* *Glycosmis pentaphylla* *Murraya paniculata*	Reported to work by reducing proinflammatory and inflammatory cytokines	[55–63]
11	Ostruthin	6-[(2E)-3,7-dimethylocta-2,6-dienyl]-7-hydroxychromen-2-one	$C_{19}H_{22}O_3$		Kurantu Kuruntu Perum Kuruntu Kadanaathi Indian coffee plum, or scramberry	*Pamburus missionis* *Flacourtia jangomas*	Known to work by suppressing iNOS and COX-2 protein expression.	[64–67]
12	3',5,7-Trihydroxy-4-methoxyflavanone or 5-O-methylscutellarein	5,7-dihydroxy-2-(3-hydroxyphenyl)-4-methoxy-4*H*-chromen-3-one	$C_{16}H_{14}O_6$		Turmeric	*Curcuma zedoaria*	Works by suppressing NF-κB activation, reduces cholesterol biosynthesis and Inhibits lipid peroxidation	[68–74]
13	7-methoxy coumarin (herniarin, 3) or Herniarin.	7-methoxychromen-2-one	$C_{10}H_8O_3$		Turmeric White mugwort Ruptureworts Ayapan	*Curcuma zedoaria* *Artemisia lactiflora,* *Herniaria* *Eupatorium Triplinerve*	Reported to work by inhbiting writhing and nociception	[75–78]

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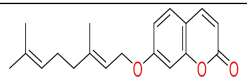
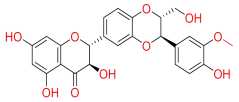
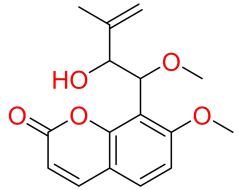
Sl No.	Coumarin compounds	IUPAC name	Formula	Structure	Plant (common names)	Scientific names	Mode of anti-inflammatory action	References
14	Auraptene	7-[(2*E*)-3,7-dimethylocta-2,6-dienoxy]chromen-2-one	$C_{19}H_{22}O_3$		Kaminmi, orange jasmine, orange jessamine, china box or mock orange	*Murraya paniculata,*	Works by reducing oxidative stress, suppresses various proinflammatory cytokines, inflammatory mediators and the enzymes involved in inflammation	[61,79–82]
15	Silibinin	(2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one	$C_{25}H_{22}O_{10}$		Milk thistle, blessed milkthistle, Marian thistle, Mary thistle, Saint Mary's thistle, Mediterranean milk thistle, variegated thistle and Scotch thistle	*Silybum marianum*	Reported to work by reducing proinflammatory and inflammatory cytokines	[83–89]
16	Murracarpin	8-(2-hydroxy-1-methoxy-3-methylbut-3-enyl)-7-methoxychromen-2-one	$C_{16}H_{18}O_5$		Kaminmi, orange jasmine, orange jessamine, china box or mock orange Curry patta, meetha neem White Himalayan Rue Orangeberry and gin berry	*Murraya paniculata,* *Murraya koenigii* *Boenninghausenia albiflora* *Glycosmis pentaphylla*	Works by inhibiting the elevation of IL-1β, TNF-α, and PGE2	[90–95]

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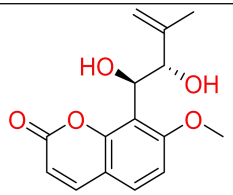
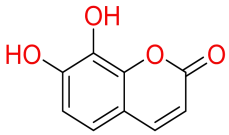
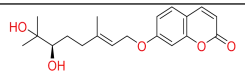
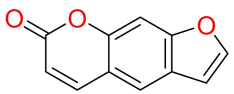
Sl No.	Coumarin compounds	IUPAC name	Formula	Structure	Plant (common names)	Scientific names	Mode of anti-inflammatory action	References
17	Murrangatin	8-[(1R,2S)-1,2-dihydroxy-3-methylbut-3-enyl]-7-methoxychromen-2-one	$C_{15}H_{16}O_5$		Curry patta, meetha neem	*Murraya koenigii* *Murraya paniculata,*	Works by downregulation of IL-1β, TNFα, PGE2, and MMP-13 etc.	[96–100]
18	Daphnetin	7,8-dihydroxychromen-2-one	$C_9H_6O_4$		Indian Paper Plant, Indian paper tree, Nepali paper plant	*Daphne papyracea*	Suppresses activation of macrophages and proinflammatory cytokines and down-regulates NF-κB-dependent signalling events. Induces expression of anti-inflammatory cytokines	[101–106]
					Himalayan Stellera	*Stellera chamaejasme*		
					sweet wormwood, sweet annie, sweet sagewort, annual mugwort	*Artemisia annua*		
19	Marmin	7-[(E,6R)-6,7-dihydroxy-3,7-dimethyloct-2-enoxy]chromen-2-one	$C_{19}H_{24}O_5$		bael (or bili) or bhel, also Bengal quince, golden apple,Japanese bitter orange,stone apple or wood apple	*Aegle marmelos*	Works by lowering nuclear factor kappa-B (NF-κB)	[107–112]
					Citron, rough lemon	*Citrus medica*		
20	Psoralen	furo[3,2-g]chromen-7-one	$C_{11}H_6O_3$		wood-apple and elephant-apple	Limonia acidissima	Works via estrogen receptor signalling pathway	[113–117]

4. Molecular mechanism of the anti-inflammatory activity of coumarins

Coumarins exhibit their anti-inflammatory activities through various molecular mechanisms. Different coumarins compounds follow different molecular mechanisms to ultimately mitigate inflammation.

As evident from study conducted on mice, scopoletin is known to have inhibitory activity on PGE2 and TNF-α overproduction, and neutrophil infiltration. Also, it is reported that scopoletin significantly attenuates the malondialdehyde (MDA) level in the edema paw of experimental mice. Thus, scopoletin inhibits the pro-inflammatory cytokines and exhibits its anti-inflammatory activity [25]. Another coumarin named Scoparone, is reported to prevent IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through the PI3K/Akt/NF-κB pathway. Scoparone is also known to suppressing the TLR4/NF-κB signalling pathway in mice which in turn mitigates inflammation, apoptosis and fibrosis associated with non-alcoholic steatohepatitis [28,29]. The other coumarin, fraxetin is reported to exhibit its anti-inflammatory activity by the mechanism of suppressing IL-1β-induced inflammation via the TLR4/MyD88/NF-κB pathway in rat chondrocytes. Also,the other molecular mechanism of the anti-inflammatory activity of fraxetin is by imparting a suppression effect on microglia-mediated neuroinflammation, and this effect is associated with the PI3K/Akt/NF-κB signalling pathway [32,33]. Fraxinol, another known coumarin compound with anti-inflammatory activity is known to reduce inflammation by the mechanism of inhibiting the T-cells and prostaglandin biosynthesis [37].

Umbelliferon, a very common coumarins compound with widely reported anti-inflammatory activity works by significantly suppressing the hepatic lipopolysaccharide binding protein, toll-like receptor 4 (TLR4), nuclear factor kappa B, and TNF-α gene expression in alcohol fed rats and thus prevents alcohol-induced inflammation in rat hepatic tissue [39]. Also, Umbelliferon is known to reduce lipopolysaccharide-induced inflammatory responses in acute lung injury by down-regulating TLR4/MyD88/NF-κB signalling [40]. Isofraxidin, another coumrin is reported to impart its anti-inflammatory activity by decreasing the lipopolysaccharide (LPS)-induced overproduction of nitric oxide (NO), prostaglandin E2 (PGE2), tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Isofraxidin is also nreported to mitigate the increased expression of inflammatory enzymes, like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), in response to LPS stimulation and thus helps to reduce LPS- induced inflammation [50,51].

Esculin, the coumarins is also a well reported anti-inflammatory coumarins. The basic molecular mechanism of action of this coumarin is reported to be by decreasing the cytokines IL-1, IL-6, ICAM-1, NO and NGAL levels in serum of diabetic rats in a dose dependent manner thus reducing the risks of microvascular complications associated with diabetes [54]. Scopolin, another aanti-inflammatory coumarins compound is known to exhibit its anti-inflammatory action by the molecular mechanism of inhibiting eicosanoid-release from ionophore-stimulated mouse peritoneal macrophages. Also, scopolin is known to reduce IL-6, VEGF and FGF-2 expressions in rat synovial tissue [62,63]. The molecular mechanism of the anti-inflammatory activity of the coumarins, Ostruthin is reported to be by suppressing LPS-induced iNOS and COX-2 protein expressions [67]. 5-O-methylscutellarein, is known to impart its anti-inflammatory potential by suppressing the NF-κB [70]. Auraptene is also known to have anti-inflammatory activity. Studies show that treatment with auraptene (10-90 μM) significantly ameliorates ROS, MDA, IL-6, and TNF-α levels. Also, studies show that Auraptene, as a pre-treatment for five days before and another three days after ischemic surgery, suppressed microglial activation, cyclooxygenase (COX)-2 expression in astrocytes, and COX-2 mRNA expression in the hippocampus. Other underlying molecular

mechanism of the anti-inflammatory activity of the coumarin auraptene is by suppressing the lipopolysaccharide-induced expression of COX-2 mRNA and the mRNA of pro-inflammatory cytokines in cultured astrocytes. It is also reported to have the capacity to interfere with inflammatory mediator secretion and to promote wound healing [81,82].

Silibinin is known to have potent anti-inflammatory activity and the underlying molecular mechanism is reported to be by altering the level of various pro-inflammatory cytokines. Studies conducted in vitro using human fetal membranes reports that the coumarins, silibinin has the ability to significantly decrease LPS-stimulated expression of IL-6 and IL-8, COX-2, and prostaglandins PGE2 and PGF2α. In primary amnion and myometrial cells, silibinin is also reported to decrease the IL-1β-induced MMP-9 expression.Preterm fetal membranes with active infection treated with silibinin shows a decrease in IL-6, IL-8 and MMP-9 expression. Fetal brains from mice treated with silibinin shows a significant decrease in LPS-induced IL-8 and ninjurin, a marker of brain injury. Other studies show that Silibinin is capable of reducing, at least in part, the levels of NF-κB and cytokines TNF-α and IL-1β in preeclamptic women. Also, Silibinin alleviates inflammation and induces apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes and has a therapeutic effect on arthritis in rats [88,89]. Murracarpin is another potent anti-inflammatory coumarin. In carrageenin pleurisy model, murracarpin is reported to effectively inhibit the elevation of IL-1β, TNF-α, and PGE2 and thus mitigate inflammation therein [95].

Another coumarins compound with reported anti-inflammatory potential is murrangatin. One of the reported molecular mechanism of the anti-inflammatory activity of murrangatin is by downregulation of IL-1β, TNFα, PGE2, and MMP-13. By this mechanism it the compound imparts chondroprotective activity, Other studies show that Murrangatin has anti-inflammatory activity against mouse RAW264.7 cells the underlying mechanism of which is by reduction of LPS-induced NO production after 24 hrs by the compound [99,100]. Daphnetin, is also another reported anti-inflammatory coumarins. Studies show that one of the mechanisms of anti-inflammatory activity of the compound is by suppression of the activation of macrophage and human alveolar epithelial cells in response to lipopolysaccharide (LPS). This in turn is related to the down-regulation of NF-κB-dependent signalling events. Also, Daphnetin treatment is reported to significantly decrease the expression of pro-inflammatory cytokines and cause increased expression of anti-inflammatory cytokines in rat SAP. Molecular analysis reveals that daphnetin reduces TLR4 expression and inhibits NF-κB signalling pathway activation. These findings demonstrate that daphnetin attenuates acute pancreatic injury by regulating the TLR4/ NF-κB signalling pathway and inflammation in rat SAP model [102,106]. Marmin is another reported coumarins compound with anti-inflammatory potential. Extracts of plants containing marmin have been reported to exhibit potent anti-inflammatory activities. Studies reveal that marmin works by lowering the nuclear factor kappa-B (NF-κB) and thus reduces inflammation[113]. The coumarin, psoralen is known to exhibit anti-inflammatory effects on synoviocytes, and mitigate monosodium iodoacetate-induced osteoarthritis. The mechanism of anti-inflammatory activity of psoralen in human periodontal ligament cells is reported to be via estrogenic receptor signalling pathway [114].

There are many more such coumarins compounds abundantly distributed in nature. The molecular mechanism of the anti-inflammatory activity of each of these coumarins are unique and varies from each other. The basic molecular mechanism of the anti-inflammatory activity of the coumarins seems to be by altering and effecting the anti-inflammatoy and pro-inflammatory cytokines associated with inflammation in various tissues.

5. Extraction, purification, and isolation of coumarins from plant sources

Coumarins are widely distributed in nature in various plants. Theses potent phyto-constituents are extracted and purified by conventional methods of phytocompounds extraction. Various extraction techniques that are in use for isolating and purifying coumarins from plants are maceration, ultrasound maceration [118]. By these techniques, basically the plant material is macerated and the plant cells are broken down releasing the cellular content which includes the coumarins compounds along with many other compounds. In certain cases, the plant material in whole or after maceration or homogenization is infused with aqueous ethanol, water, methanol, ethyl acetate, chloroform, diethyl ether, or other solvents etc. [119,120]. The coumarins compounds thus gets in dissolution into the suitable solvent and is then subjected to further purification process. The prime technique used commonly for purification and isolation of such phytocompounds as the coumarins is chromatography. Mostly various types of column chromatography is utilized coupled with or in some cases followed by high throughput liquid chromatography which is often coupled with fine analytical instruments like photodiode array detector (DAD) etc. After the purified fraction is compared against standards and collected from those analytical techniques, those are further subjected to finer analysis for understanding and interpretation of the composition and prediction of the molecular structure of the compounds. Techniques like MALDI TOFF, Scanning Electron microscopy, X-Ray Crystallography etc. are used for structural analysis of the purified coumarins. Some of the techniques used for purification and isolation of the coumarins involve utilization of various sophisticated analytical instruments like high performance liquid chromatography with UV detector (HPLC-UV) [121], reverse-phase high-performance liquid chromatographic method (RP-HPLC) coupled with a photodiode array detector (DAD) [122] etc., Also, other instruments like Scanning Electron Microscope (SEM)[123], Soxhelation, Ultrasonic-assisted response surface methodology (RSM) [123] etc. are used for extended procedures of extract1ion of coumarins from various plant sources.

6. Benefits of the use of coumarin compounds

Natural Coumarin compounds come from plant sources and are thus devoid of much or any side effects unlike synthetic pharmaceutical compounds and formulations. These natural compounds can be used in combination with other pharmaceutical combinations. Studies reveal that most of the coumarins compounds exhibit anti-inflammatory as well as antioxidant activities. Hence, this makes these natural bioactive coumarins a perfect and potent candidate for developing potential anti-inflammatory drug formulations with dual benefits [124]. On one hand these act as effective anti-inflammatory agents impacting and regulating various pathways associated with pain and inflammation and on the other hand coumarins by virtue of their antioxidant potential reduces the oxidative stress mediated complications of inflammation and also is easy to be processed and metabolized by our liver. Overall, the properties of natural bioactive coumarins make them safer anti-inflammatory agents compared to other anti-inflammatory agents [124]. Studies show that non-steroidal anti-inflammatory drugs (NSAIDs) like piroxicam may be harsh on the gastric mucosal lining and may induce gastric ulcers. Whereas, these natural coumarin compounds from the plants of Indo-gangetic possess antioxidant potentials and they have been reported to be protective on gastric mucosa and are known not to induce oxidative stress there in unlike NSAIDs [124]. In addition to these magical miraculous properties of the natural coumarins compounds, they have been found to be adequately bio-available [124] which further qualifies them as suitable candidates for developing anti-inflammatory formulations. Coumarins are known to scavenge reactive oxygen species and thus

are capable of effecting and influencing processes involving free radicals-induced injury and damages [125]. With all these benefits, coumarin compounds being available from natural resources can be easily isolated and can be used for developing better derivatives if needed and thus can be immensely utilised for developing potent anti-inflammatory pharmaceutical formulations with minimum side effects. Also, the lead coumarins compounds being mostly extracted from natural sources, it is expected that the anti-inflammatory drugs developed using natural coumarins and their derivatives will be potent, safer, better, cost effective and affordable.

7. Coumarin compounds from plants of other regions

The micro and macronutrient composition of the soil varies as per the geographical regions. Thus, the plants growing in the indo-gangetic region and those growing in other regions vary in their composition. The potency of these bioactive phytocompounds are also reported to vary depending on the variation of the geographical region and soil composition. In vitro studies conducted on *Murraya koenigi* collected from different districts of the state of West Bengal, India is reported to have varied in their antioxidant potential [126]. Depending on the region , the climate and the soil composition, certain plants grow only in specific regions. Coumarins from those plants growing in other regions than the indo-gangetic plain have also been reported to exhibit potent anti-inflammatory activities. Thus, some of the coumarins compounds which are found in specific plants which do not grow in the indo-gangetic region are available in the plants which grow in other regions. High concentrations of coumarins are reported to be present in plants like *Justicia pectoralis* [127] which grows in the tropical areas of the Americas, including South and Central America and also grows in some Caribbean islands like Trinidad and Tobago [128], *Dipteryx odorata* (old name *Coumarouna odorata)* (tonka bean) (Fabaceae/Leguminosae) [129] which is also a tropical South American plant [130], Studies report high content of coumarins in plants like vanilla grass (*Anthoxanthum odoratum*) [131] which is native to acidic grassland in Eurasia and northern Africa [131] and many others. Studies also report abundant distribution of coumarins compounds in various plants from several plants grown exclusively in China and other parts of Eurasia. Those coumarins have potent bioactivities including anti-inflammatory activities. Phytoconstituents of plants like *Cinnamomum cassia* etc. has been evaluated to have potent anti-inflammatory activities in various experimental models and those plants have also been reported to be rich in coumarins [130]. Mostly, the type of coumarin compounds found in the plants from Indo-Gangetic region differ in their chemical structure from those obtained from the plants grown in other regions. Also, the biopotential of the same coumarins compounds obtained from same or different plant may vary depending on the composition of the soil the plant has grown in.

8. Summary and conclusion

Investigations on the anti-inflammatory property of the natural coumarins compounds from various plants of the indo-gangetic plain delineated the basic mechanism to involve lowering of various pro-inflammatory cytokine levels including NF-κB and by altering the levels of prostaglandins [68,78]. Some others alter the quantity of cytokines which are involved in the mechanism of inducing pain and inflammation [69–75]. Studies reveal that potent antioxidant activities complement the anti-inflammatory potential of the natural coumarins and their derivatives [124,125]. Extensive research findings around the world involving investigations on the identification, isolation and anti-inflammatory potentials of the coumarin compounds from various

regional endogenous plants and their derivatives, confirms the possibility of discerning coumarins as highly potent, cost effective and safe future anti-inflammatory therapeutic agents.

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Conflict of Interests

We declare no conflicts of interest in the paper.

References

1. Bansal Y, Sethi P, Bansal G (2013) Coumarin: a potential nucleus for anti-inflammatory molecules. *Med Chem Res* 22: 3049–3060. https://doi.org/10.1007/s00044-012-0321-6
2. Musa MA, Cooperwood JS, Khan MO (2008) A review of coumarin derivatives in pharmacotherapy of breast cancer. *Curr Med Chem* 15: 2664–2679.
3. Kontogiorgis CA, Hadjipavlou-Litina DJ (2005) Synthesis and antiinflammatory activity of coumarin derivatives. *J Med Chem* 48: 6400–6408. https://doi.org/10.1021/jm0580149
4. Kirsch G, Abdelwahab AB, Chaimbault P (2016) Natural and Synthetic Coumarins with Effects on Inflammation. *Molecules* 21: 1322. https://doi.org/10.3390/molecules21101322
5. Medzhitov R (2010) Inflammation 2010: new adventures of an old flame. *Cell* 140: 771–776.
6. Nathan C, Ding A (2010) Nonresolving inflammation. *Cell* 140: 871–882.
7. Chen L, Deng H, Cui H, et al. (2017) Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* 9: 7204–7218.
8. Jabbour HN, Sales KJ, Catalano RD, et al. (2009) Inflammatory pathways in female reproductive health and disease. *Reprod* 138: 903–919.
9. Omoigui S (2007) The biochemical origin of pain: the origin of all pain is inflammation and the inflammatory response. Part 2 of 3-inflammatory profile of pain syndromes. *Med Hypotheses* 69: 1169–1178.
10. Rostom B, Karaky R, Kassab I, et al. (2022) Coumarins derivatives and inflammation: Review of their effects on the inflammatory signaling pathways. *Eur J Pharmacol* 922: 174867.
11. Witaicenis A, Seito LN, da Silveira Chagas A, et al. (2014) Antioxidant and intestinal anti-inflammatory effects of plant-derived coumarin derivatives. *Phytomedicine* 21: 240–246.
12. Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, et al. (2004) Natural and synthetic coumarin derivatives with anti-inflammatory/ antioxidant activities. *Curr Pharm Des* 10: 3813–3833.
13. Narayanaswamy R, Veeraragavan V (2020) *Chapter 8-Natural products as antiinflammatory agents, Bioactive Natural Products in Studies, In: Natural Products Chemistry,* Editor(s): Atta-ur-Rahman, Elsevier, 67: 269–306.
14. Borges M F, Roleira F M, Milhazes N J, et al. (2009) Simple coumarins: privileged scaffolds in medicinal chemistry. *Front Med Chem* 4: 23–85. https://doi.org/10.2174/978160805207310904010023

15. Coumarin in Cinnamon, Cinnamon-Containing Foods and Licorice Flavoured Foods. Government of Canada.2015. Available from: https://inspection.canada.ca/food-safety-for-industry/food-chemistry-and-microbiology/food-safety-testing-bulletin-and-reports/coumarin/eng/1568641632892/1568641633299.
16. Bioactive Natural Products. Studies in Natural Products Chemistry, 2000. Available from: https://www.sciencedirect.com/topics/food-science/licorice.
17. Tava A (2001) Coumarin-containing grass: volatiles from sweet vernalgrass (*Anthoxanthum odoratum L.*). *J Essent Oil Res* 13: 367–370. https://doi.org/10.1080/10412905.2001.9712236
18. Sharopov F, Setzer WN (2018) Medicinal plants of Tajikistan. In: Egamberdieva D., Öztürk M., editors. *Vegetation of Central Asia and environs*. Switzerland: Springer Nature, 163–210.
19. Sharifi-Rad J, Cruz-Martins N, López-Jornet P, et al. (2021) Natural Coumarins: Exploring the Pharmacological Complexity and Underlying Molecular Mechanisms. *Oxid Med Cell Longev*. 2021: 6492346. https://doi.org/10.1155/2021/6492346
20. Garg SS, Gupta J, Sharma S, et al. (2020) An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. *Eur J Pharm Sci* 152: 105424.
21. Matos MJ, Santana L, Uriarte E, et al. (2015) Coumarins-An Important Class of Phytochemicals. *Phytochemicals-Isolation, Characterisation and Role in Human Health* 25: 533–538.
22. Han XL, Wang H, Zhang ZH, et al. (2015) nStudy on Chemical Constituents in Seeds of Datura metel from Xinjiang. *Zhong Yao Cai = Zhongyaocai = J Chinese Med Mater (in Chinese)* 38: 1646–1648.
23. Ding Z, Dai Y, Hao H, et al. (2008) Anti-Inflammatory Effects of Scopoletin and Underlying Mechanisms. *Pharm Biol* 46: 854–860.
24. Chang TN, Deng JS, Chang YC, et al. (2012) Ameliorative Effects of Scopoletin from *Crossostephium chinensis* against Inflammation Pain and Its Mechanisms in Mice. *Evid Based Complement Alternat Med* 2012: 595603.
25. Debaggio T, Tucker AO (2009) *The Encyclopedia of Herbs, A Comprehensive Reference to Herbs of Flavor and Fragrance*, Timber Press.
26. National Center for Biotechnology Information, PubChem Compound Summary for CID 8417.Scoparone,2022.Availablefrom: https://pubchem.ncbi.nlm.nih.gov/compound/Scoparone.
27. *Artemisia absinthium*. Flora Italiana, 2022. Available from: http://luirig.altervista.org/.
28. Lu C, Li Y, Hu S, et al. (2018) Scoparone prevents IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through the PI3K/Akt/NF-κB pathway. *Biomed Pharmacother* 106: 1169–1174.
29. Liu B, Deng X, Jiang Q, et al. (2019) Scoparone alleviates inflammation, apoptosis and fibrosis of non-alcoholic steatohepatitis by suppressing the TLR4/NF-κB signaling pathway in mice. *Int Immunopharmacol* 75: 105797.
30. National Center for Biotechnology Information, PubChem Compound Summary for CID 5273569.Fraxetin,2022.Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Fraxetin.
31. Li J, Lin B, Wang G, et al. (2012) Chemical constituents of Datura stramonium seeds. *Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China J Chinese Materia Medica (in Chinese)* 37: 319–322.
32. Wang Q, Zhuang D, Feng W, et al. (2020) Fraxetin inhibits interleukin-1β-induced apoptosis, inflammation, and matrix degradation in chondrocytes and protects rat cartilage in vivo. *Saudi Pharm J* 28:1499–1506.
33. Deng S, Ge J, Xia S, et al. (2022) Fraxetin alleviates microglia-mediated neuroinflammation after ischemic stroke. *Ann Transl Med* 10: 439.

34. National Center for Biotechnology Information, PubChem Compound Summary for CID 3047739. Fraxinol, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Fraxinol.
35. Mountain Cherry. Flowers of India, 2023. Available from: http://www.flowersofindia.net/catalog/slides/Mountain%20Cherry.html.
36. Soto-Blanco B (2022) Chapter 12-Herbal glycosides in healthcare,Editor(s): Subhash C. Mandal, Amit Kumar Nayak, Amal Kumar Dhara, *Herbal Biomolecules in Healthcare Applications*, Academic Press, 239–282.
37. Sankara Rao K, Navendu Page, Deepak Kumar. Pan India Bouquets, 2020. Available from: http://flora-peninsula-indica.ces.iisc.ac.in/pan/plants.php?
38. National Center for Biotechnology Information, PubChem Compound Summary for CID 5281426.Umbelliferone,2022.Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Umbelliferone.
39. Sim MO, Lee HI, Ham JR, et al. (2015) Anti-inflammatory and antioxidant effects of umbelliferone in chronic alcohol-fed rats. *Nutr Res Pract 9*: 364–369.
40. Wang D, Wang X, Tong W, et al. (2019) Umbelliferone Alleviates Lipopolysaccharide-Induced Inflammatory Responses in Acute Lung Injury by Down-Regulating TLR4/MyD88/NF-κB Signaling. *Inflammation* 42: 440–448.
41. Selim YA, Ouf NH (2012) Anti-inflammatory new coumarin from the *Ammi majus L Org Med Chem Lett* 2: 1. https://doi.org/10.1186/2191-2858-2-1
42. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 238946, 6-Hydroxy-7-methoxy-4-methyl-2H-chromen-2-one, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/6-Hydroxy-7-methoxy-4-methyl-2H-chromen-2-one.
43. El-Haggar R, Al-Wabli RI (2015) Anti-inflammatory screening and molecular modeling of some novel coumarin derivatives. *Molecules* 20: 5374–5391.
44. Quattrocchi U (2012) *Ammi majus*, CRC World Dictionary of Medicinal and Poisonous Plants: Common Names. Scientific Names, Eponyms, Synonyms, and Etymology (5 Volume Set), CRC Press, 244.
45. Walliser J (2014) *Ammi majus,* Attracting Beneficial Bugs to Your Garden: A Natural Approach to Pest Control. Portland, Oregon: Timber Press, 114–115.
46. Elgamal MHA, Shalaby NMM, Duddeck H, et al. (2013) Coumarins and coumarin glucosides from the fruits of *Ammi majus*. *Phytochemistry* 34: 819–823. https://doi.org/10.1016/0031-9422(93)85365-X
47. 4-methylumbellione. Merck, 2022. Available from: https://www.sigmaaldrich.com/IN/en/product/aldrich/m1381.
48. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 5318565, Isofraxidin, 2023. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Isofraxidin.
49. Yamazaki T, Tokiwa T (2010) Isofraxidin, a coumarin component from Acanthopanax senticosus, inhibits matrix metalloproteinase-7 expression and cell invasion of human hepatoma cells. *Bio Pharm Bull* 33: 1716–1722.
50. Jin J, Yu X, Hu Z, et al. (2018) Isofraxidin targets the TLR4/MD-2 axis to prevent osteoarthritis development. *Food Funct* 9: 5641–5652.
51. Jacqueline N (2006) Chinese Celery. *Vegetables and Vegetarian Foods* 13: 15–34.

52. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 5281417. Esculin, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Esculin.
53. Taxon: Hordeum vulgare L. subsp. spontaneum (K. Koch) Thell. GRIN Taxonomy for Plants. GRIN, 2022. Available from: https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=4513.
54. Wang YH, Liu YH, He GR, et al. (2015) Esculin improves dyslipidemia, inflammation and renal damage in streptozotocin-induced diabetic rats. *BMC Complement Altern Med* 15: 402.
55. National Center for Biotechnology Information. PubChem Compound Summary for CID 439514. Scopolin, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Scopolin.
56. Taxon. *Arabidopsis thaliana* (L.) Heynh, 2022. Available from: http://www.tn-grin.nat.tn/gringlobal/taxon/taxonomydetail?id=3769.
57. Döll S, Kuhlmann M, Rutten T, et al. (2018) Accumulation of the coumarin scopolin under abiotic stress conditions is mediated by the *Arabidopsis thaliana* THO/TREX complex. *Plant J* 93: 431–444.
58. Artemisia minor. EFolra of India, 2022. Aviailable from: https://efloraofindia.com/2022/07/23/artemisia-minor/.
59. Scopolin. Wikipedia, 2022. Available from: https://en.wikipedia.org/wiki/Scopolin.
60. *Glycosmis pentaphylla*. 2022. Available from: https://indiabiodiversity.org/species/show/32607
61. Zich FA, Hyland BPM, WhiffenT, et al. (2020) *Murraya paniculata*. Aus*tralian Tropical R*ainforest Plants Edition 8 (RFK8). Centre for Australian National Biodiversity Research (CANBR), Australian Government.
62. Silván AM, Abad MJ, Bermejo P, et al. (1999) Antiinflammatory activity of coumarins from *Santolina oblongifolia*. *J Nat Prod* 59: 1183–1185.
63. Pan R, Dai Y, Gao X, et al. (2009) Scopolin isolated from Erycibe obtusifolia Benth stems suppresses adjuvant-induced rat arthritis by inhibiting inflammation and angiogenesis. *Int Immunopharmacol* 9: 859–869.
64. India Biodiversity Portal, 2022. Available from: https://indiabiodiversity.org/species/show/250754#habitat-and-distribution.
65. *Flacourtia jangomas* (Lour.) Raeuschel, Pacific Island Ecosystems at Risk (PIER), 2022. Available from: http://www.hear.org/pier/species/flacourtia_jangomas.htm.
66. Ayurvedic Medicinal Plants of Sri Lanka Compendium version 3, 2022. Aailable from: http://www.instituteofayurveda.org/plants/plants_detail.php?i=1188&s=local_name.
67. Tuan Anh HL, Kim DC, Ko W, et al. (2017) Anti-inflammatory coumarins from *Paramignya trimera*. *Pharm Biol* 55: 1195–1201.
68. National Center for Biotechnology Information, PubChem Compound Summary for CID69304032,3',5,7-Trihydroxy-4-methoxyflavanone, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3_5_7-Trihydroxy-4-methoxyflavanone.
69. 357-trihydroxy-4-methoxyflavone, 2022. Available from: https://www.biosynth.com/p/FT66491/491-54-3-357-trihydroxy-4-methoxyflavone.
70. Lima JCS, de Oliveira RG, Silva VC, et al. (2018) Anti-inflammatory activity of 4',6,7-trihydroxy-5-methoxyflavone from *Fridericia chica* (Bonpl.) L.G.Lohmann. *Nat Prod Res* 34: 726–730.
71. Rahayu D, Setyani D, Dianhar H, et al. (2020) Phenolic Compounds From Indonesian White Turmeric *(Curcuma Zedoaria*) Rhizomes. *Asian J Pharm Clin Res* 2020*:* 194–198.

72. Hardigree AA, Epler JL (1978) Comparative mutagenesis of plant flavonoids in microbial systems. *Mutat Res/Genet Toxicol 58*: 1109–1114.
73. Wattenberg LW, Page MA, Leong JL (1968) Induction of increased benzpyrene hydroxylase activity by flavones and related compounds. *Cancer Res 28*: 934–936.
74. 3',5,7-Trihydroxy-4'-methoxyflavanone. Alfa Aesar, 2022. Available from: https://www.alfa.com/en/catalog/B20528/.
75. Botanical Survey of India. Government of India, Ministry of Environment, Forest & ClimateChange,2022.Availablefrom: https://efloraindia.bsi.gov.in/eFlora/speciesDesc_PCL.action?species_id=28580.
76. National Center for Biotechnology Information. PubChem Compound Summary for CID 10748,7-Methoxycoumarin,2022.Availablefrom: https://pubchem.ncbi.nlm.nih.gov/compound/7-Methoxycoumarin.
77. Cheriyan BV Sr, Kadhirvelu P Sr, Nadipelly J Jr, et al. (2017) Anti-nociceptive Effect of 7-methoxy Coumarin from *Eupatorium Triplinerve vahl* (Asteraceae). *Pharmacogn Mag* 13: 81–84.
78. Gurib-Fakim A, Brendler T (2004) *Medicinal and aromatic plants of Indian Ocean Islands: Madagascar, Comoros, Seychelles and Mascarenes*. Medpharm GmbH Scientific Publishers.
79. National Center for Biotechnology Information. PubChem Compound Summary for CID 1550607, Auraptene, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Auraptene.
80. Askari VR, Rahimi VB, Zargarani R, et al. (2021) Anti-oxidant and anti-inflammatory effects of auraptene on phytohemagglutinin (PHA)-induced inflammation in human lymphocytes. *Pharmacol Rep* 73: 154–162.
81. Okuyama S, Morita M, Kaji M, et al. (2015) Auraptene Acts as an Anti-Inflammatory Agent in the Mouse Brain. *Molecules* 20: 20230–20239. https://doi.org/10.3390/molecules201119691
82. La VD, Zhao L, Epifano F, et al. (2013) Anti-inflammatory and wound healing potential of citrus auraptene. *J Med Food* 16: 961–964.
83. National Center for Biotechnology Information. PubChem Compound Summary for CID 31553,Silibinin,2022.Availablefrom: https://pubchem.ncbi.nlm.nih.gov/compound/Silibinin.
84. BSBI List (xls). Botanical Society of Britain and Ireland. Archived from the original (xls) on , 2022. Available from: https://bsbi.org/.
85. Xin W, Xin W, Zhen Z, et al. (2020) Health Benefits of *Silybum marianum*: Phytochemistry, Pharmacology, and Applications. *Agric. Food Chem*. 68: 11644–11664. https://doi.org/10.1021/acs.jafc.0c04791
86. Silibinin. Wikipedia, 2022. Available from: https://en.wikipedia.org/wiki/Silibinin.
87. Lim R, Morwood CJ, Barker G, et al. (2014) Effect of silibinin in reducing inflammatory pathways in *in vitro* and *in vivo* models of infection-induced preterm birth. *PLoS One* 9: e92505.
88. Giorgi VS, Peracoli MT, Peracoli JC, et al. (2012) Silibinin modulates the NF-κb pathway and pro-inflammatory cytokine production by mononuclear cells from preeclamptic women. *J Reprod Immunol*. 95: 67–72.
89. Tong WW, Zhang C, Hong T, et al. (2018) Silibinin alleviates inflammation and induces apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes and has a therapeutic effect on arthritis in rats. *Sci Rep* 8: 3241.
90. National Center for Biotechnology Information (2022) PubChem Compound Summary for CID 5319464, Murracarpin. Retrieved September 17, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Murracarpin.

91. Tian-Shung W, Meei-Jen L, Chang-Sheng K (1989) Coumarins of the flowers of *Murraya paniculata. Phytochemistry* 28: 293–294.
92. Shi WM, Liu HQ, Li LF,et al. (2015) The anti-inflammatory activity of a natural occurring coumarin: Murracarpin. By. Medicine Sciences and Bioengineering. 1st Editio, Imprint CRC Press, 6.
93. White Himalayan Rue. Flowers of India, 2022. http://www.flowersofindia.net/catalog/slides/White%20Himalayan%20Rue.html.
94. *Glycosmis pentaphylla*. *Germplasm Resources Information Network (GRIN)*. Agricultural Research Service (ARS), United States Department of Agriculture (USDA), 2020. Available from : https://www.ars-grin.gov/.
95. Md Mubarak H, Faiza T, Md M, et al. (2017) 7-Methoxy-8-Prenylated Coumarins from *Murraya koenigii (Linn.) Spreng*. *Dhaka Univ J Pharm Sci* 15: 155.
96. National Center for Biotechnology Information (2022). Pub Chem Compound Summary for CID 181514, Murrangatin, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Murrangatin.
97. Longhuo W, Li J, Guo X, et al. (2013) Chondroprotective evaluation of two natural coumarins: murrangatin and murracarpin. *J Intercult Ethnopharmacol* 2: 91–98. https://doi.org/10.5455/jice.20130313082010
98. *Murraya paniculata (L.) Jack*. 2022. Available from: https://apps.lucidcentral.org/rainforest/text/entities/murraya_paniculata.htm.
99. Long W, Wang M, Luo X, et al. (2018) Murrangatin suppresses angiogenesis induced by tumor cell-derived media and inhibits AKT activation in zebrafish and endothelial cells. *Drug Des Devel Ther* 12: 3107–3115. https://doi.org/10.2147/DDDT.S145956
100. National Center for Biotechnology Information. PubChem Bioassay Record for Bioactivity AID 1204915-SID 312393603, Bioactivity for AID 1204915 - SID 312393603, Source: ChEMBL, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/bioassay/1204915#sid=312393603.
101. National Center for Biotechnology Information (2022) PubChem Compound Summary for CID 5280569, Daphnetin, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Daphnetin.
102. Yu WW, Lu Z, Zhang H, et al. (2014) Anti-inflammatory and protective properties of daphnetin in endotoxin-induced lung injury. *J Agric Food Chem* 62: 12315–12325.
103. Indian Paper Plant. Flowers of India, 2022. Available from: http://www.flowersofindia.net/catalog/slides/Indian%20Paper%20Plant.html.
104. Kim M, Lee H, Randy A, et al. (2017) Stellera chamaejasme and its constituents induce cutaneous wound healing and anti- inflammatory activities OPEN. *Scientific Reports* 7. https://doi.org/10.1038/srep42490
105. Himalayan *Stellera*, 2022. Available from: https://www.flowersofindia.net/catalog/slides/Himalayan%20Stellera.html.
106. Liu Z, Liu J, Zhao K, et al. (2016) Role of Daphnetin in Rat Severe Acute Pancreatitis Through the Regulation of TLR4/NF-[Formula: see text]B Signaling Pathway Activation. *Am J Chin Med* 44(1):149–163.
107. Murthy HN, Bhat MA, Dalawai D (2019) Bioactive Compounds of Bael *(Aegle marmelos* (L.) Correa). In: Murthy, H., Bapat, V. (eds) Bioactive Compounds in Underutilized Fruits and Nuts. Reference Series in Phytochemistry. Springer, Cham. https://doi.org/10.1007/978-3-030-06120-3_35-1
108. "M.M.P.N.D.-Sorting Aegle names", 2022. Available from: https://unimelb.edu.au.

109. Aegle marmelos (L.) Correa, 2023. Available from: https://eol.org/pt-BR/pages/483583/articles.
110. Davidson, Alan (2014). Tom Jaine (ed.). The Oxford Companion to Food. Illustrated by Soun Vannithone (3rd ed.). Oxford University Press, 191.
111. Benni JM, Jayanthi MK, Suresha RN (2011) Evaluation of the anti-inflammatory activity of Aegle marmelos (Bilwa) root. *Indian J Pharmacol* 43: 393–397.
112. Yun-Fang H, Si-Wen Q, Li Y, et al. (2021) Marmin from the blossoms of Citrus maxima (Burm.) Merr. exerts lipid-lowering effect via inducing 3T3-L1 preadipocyte apoptosis. *Journal of Funct Foods* 82: 104513.
113. Wang C, Al-Ani MK, Sha Y, et al. (2019) Psoralen Protects Chondrocytes, Exhibits Anti-Inflammatory Effects on Synoviocytes, and Attenuates Monosodium Iodoacetate-Induced Osteoarthritis. *Int J Biol Sci* 15: 229–238.
114. Li H, Xu J, Li, X, et al. (2021) Anti-inflammatory activity of psoralen in human periodontal ligament cells via estrogen receptor signaling pathway. *Sci Rep* 11: 8754.
115. National Center for Biotechnology Information. PubChem Compound Summary for CID6199,Psoralen, 2022. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Psoralen.
116. Mirjana L, Martina L, Drago S, et al. (2020) Coumarins in Food and Methods of Their Determination. Foods 9: 645.
117. Limoniaacidissima, 2023. Avilable from: https://www.scientificlib.com/en/Biology/Plants/Magnoliophyta/LimoniaAcidissima01.html.
118. Thada R, Chockalingam S, Dhandapani RK, et al. (2013) Extraction and Quantitation of Coumarin from Cinnamon and its Effect on Enzymatic Browning in Fresh Apple Juice: A Bioinformatics Approach to Illuminate its Antibrowning Activity. *J Agric Food Chem* 61: 5385–5390.
119. Leal LKAM, Ferreira AAG, Bezerra GA, et al. (2000) Antinociceptive, anti-inflammatory and bronchodilator activities of Brazilian medicinal plants containing coumarin: A comparative study. *J Ethnopharmacol* 70: 151–159. https://doi.org/10.1016/S0378-8741(99)00165-8
120. Celeghini RMS, Vilegas JHY, Lanças FM (2001) Extraction and quantitative HPLC analysis of coumarin in hydroalcoholic extracts of *Mikania glomerata* Spreng. ("guaco") leaves. *J Braz Chem Soc* 12: 706–709.
121. Maja M, Igor J, Dragica S, et al. (2017) Screening of Six Medicinal Plant Extracts Obtained by Two Conventional Methods and Supercritical CO2 Extraction Targeted on Coumarin Content, 2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Capacity and Total Phenols Content. *Molecules* 22: 348.
122. Skalicka-Woźniak K, Głowniak K (2012) Pressurized liquid extraction of coumarins from fruits of Heracleum leskowii with application of solvents with different polarity under increasing temperature. *Molecules* 17: 4133–4141.
123. Wang T, Li Q (2022) DES Based Efficient Extraction Method for Bioactive Coumarins from Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. *Separations 9*: 5.
124. Arora RK, Kaur N, Bansal Y, et al. (2014) Novel coumarin-benzimidazole derivatives as antioxidants and safer anti-inflammatory agents. *Acta Pharm Sin B* 4: 368–375.
125. Hadjipavlou-Litina JD, Litinas EK, Kontogiorgis C (2007) The Anti-inflammatory Effect of Coumarin and its Derivatives. *Anti-Inflamm Anti-Allergy Agents in Med Chem* 6: 293–306.
126. Debosree G, Elina M, Syed BF, et al. (2012) In vitro studies on the antioxidant potential of the aqueous extract of Curry leaves *(Murraya koenigii L.*) collected from different parts of the state of West Bengal. *Indian J Physiol Allied Sci* 66: 77–95.

127. Luzia L, Aline S, Glauce V (2017) *Justicia pectoralis*, a coumarin medicinal plant have potential for the development of antiasthmatic drugs? *Revista Brasileira de Farmacognosia* 27. https://doi.org/10.1016/j.bjp.2017.09.005
128. Rohini K, Srikumar PS (2014) Therapeutic Role of Coumarins and Coumarin-Related Compounds. *J Thermodyn Catal* 5: 2. https://doi.org/10.4172/2157-7544.1000130
129. *Dipteryx odorata*, 2023. Available from: https://tropical.theferns.info/viewtropical.php?id=Dipteryx+odorata.
130. Liao JC, Deng JS, Chiu CS, et al. (2012) Anti-Inflammatory Activities of *Cinnamomum cassia* Constituents In Vitro and In Vivo. *Evid Based Complement Alternat Med* 2012: 429320. https://doi.org/10.1155/2012/429320
131. *Anthoxanthum odoratum,* 2022. Available from: https://en.wikipedia.org/wiki/Anthoxanthum_odoratum.

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