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A SYSTEMATIC REVIEW OF COUMARINS, ITS USE, BIOAVAILABILITY AND INTERACTION WITH PHARMACOLOGICAL ACTIVITIES

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Abstract

Coumarins are one of the most important classes of heterocycles that occupies prime position in synthetic and pharmaceutical chemistry due to their diverse applications. The Tonka bean, which was first isolated in 1820, gave rise to the French word "coumarou," which gave rise to the name "coumarins". All coumarins are members of the benzopyrone family, which is made up of benzene rings connected to pyrone rings. The benzopyrones can be subdivided into the benzo-alfa-pyrones to which the coumarins belong and the benzo-gama-pyrones. Since there aren't many studies on coumarin bioavailability, more research is required to examine the bioavailability of several coumarins that have previously shown strong biological activity. Many medicinal plants are source of coumarin. Coumarins, found in a variety of plants from different biodiversity regions. We will try to enumerate the natural coumarin compounds here, along with their occurrence, abundance and potential for use as pharmacological treatments. The biosynthesis of coumarin is related to the higher plants. However, it was also found that several microorganisms such as fungi and bacteria may produce coumarin compounds through specific metabolic routes. Natural coumarins shows a wide spectrum of pharmacological activities including anti-inflammatory, anticancer, antioxident, antiviral and Alzheimer's disease inhibition.

1.Introduction

Coumarin have been studied for more then 200 years. Their name derived from the species Coumarouna odorata Aube (Dipteryx odorata) commonly tonka beans , from which they were first time isolated (Womer et al., 1991).

Fig.1: Pictures Of Tonka Beans

With its chemical formula of 2H-1-benzopyran-2-one, coumarin was initially discovered as an oxygen heterocycle in the 1820s and is well-known for its scent of freshly cut hay or vanilla. It was initially separated from tonka beans in 1822 Gleye et al., 2003. Numerous plants contain the naturally occurring volatile active chemical coumarin. It has a melting point of 341-344K and is a white crystal with a vanilla-like scent at room temperature (Muray, 1991).

Because coumarins are beneficial as physiologically active agents, they belong to an elite class of naturally occurring compounds that play a specific function in nature. As a result, interest in their chemistry can not be ignored. They are common secondary plant metabolites that have a variety of interesting biological characteristics. Over 1800 different naturally occurring coumarins have been identified. The aromatic ring of most of these coumarins is mono- or deoxygenated (R.D.H et al., 2002).

Coumarins are present as free state in plants owing to their polar structure, and they shows blue fluorescence on UV-light absorption(Stefanachi et al., 2018).

1. Structure

The structure of coumarin consists of an aromatic ring.Coumarin is classified as a member of the benzopyrone family of com pounds, all of which consist of a benzene ring joined to a pyrone ring (Ojala 2001).

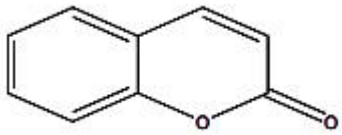


Fig.2: Chemical Structure Of Coumarin

A form of heterocyclic chemical known as benzopyrone is created when the pyrone ring fuses with the benzene nucleus. There are two distinct kinds of benzopyrone that are known to be present. They are Benzo-α-pyrone fig 1 commonly called as coumarin, Benzo-γ-pyrone fig 2 commonly called as chromones, which differs from each other only in the position of the carbonyl group in the pyrone ring (Gleye et al., 2003).

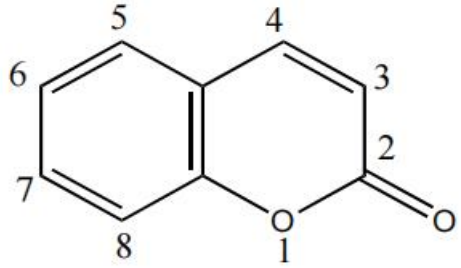


Fig.3: a-Benzopyrone

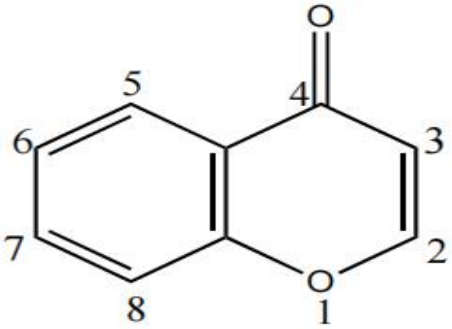
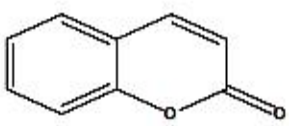
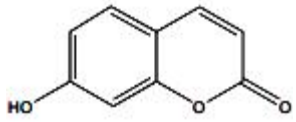
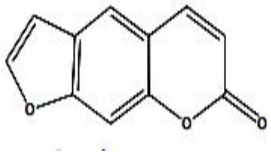
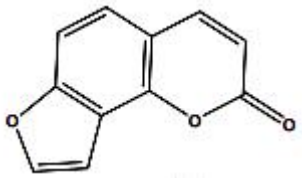
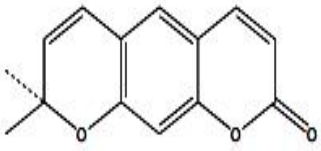
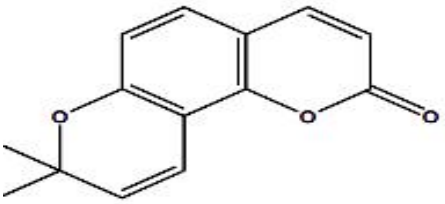
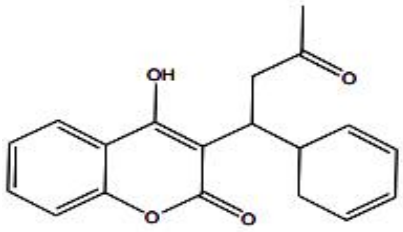


Fig.4: ϒ Benzopyrone

2. Classification of coumarins

(Lacy On the bases of chemical composition and substitution, coumarins have been divided into four subtypes: simple coumarin, furanocoumarins, pyranocoumarins and the pyrone substituted coumarins. Members of the pyranocoumarin family have six members, however they are similar to furanocoumarins. 4-hydroxy coumarin is the fourth kind of pyrone substituted coumarin and Lacy Kennedy 2004).

Classification	Structural features	Examples
Simple Coumarins	Hydroxylated, alkylated, or alkoxylated on benzene ring	 **Coumarin**  **7-hydroxy coumarin**
Furanocoumarins	Five membered furan ring attached to the benzene ring (linear or angular type)	 **Psoralen**  **Angelicin**
Pyranocoumarins	Six membered pyran ring attached to the benzene ring (linear or angular type)	 **Xanthyletin**  **Seselin**
Pyrone-substituted coumarins	Substitution on pyron ring at 3 or 4-C positions	 **Warfarin**

3. Occurance:

Most plants, fungi and bacteria contain large quantities of coumarins (1,2-benzopyrone), which are significant secondary metabolites Lacy and kennedy 2004. Many different types of plants including tonka bean, sweet woodruff, vanilla grass and sweetgrass naturally contain coumarin (Carneiro et al., 2020).

A wide range of plants including cassia, lavender, yellow sweet clover and woodruff, naturally contain coumarin (1,2-benzopyrone). Some essential oils have a high concentration of it, including lavender and cinnamon bark oils. In addition, coumarin may be found in green tea, fruits (e.g cloud berry and bilberry) and other foods (Fesser and Ellis 1974).

Recently six new minor coumarins have been isolated from the fruits and the stem bark of *Calophyllum dispar* (Clusiaceae). The genus *Calophyllum*, which comprises 200 species, is widely

spread in the tropical rain forest where many species are used in folk medicine (Guilet et al., 2001).

Coumarins are often found in the plants of *Guttiferae*, *Oleaceae*, *Apiaceae*, *Umbelliferae*, *Caprifoliaceae*, *Clusiaceae*, *Rutaceae*, and *Nyctaginaceae* families. Prusty and Kumar 2019. They can be present in free form or conjugated with other molecules as glycosides (Yang et al., 2009).

They are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and cloudberry), green tea and other foods such as chicory (Lake 1999).

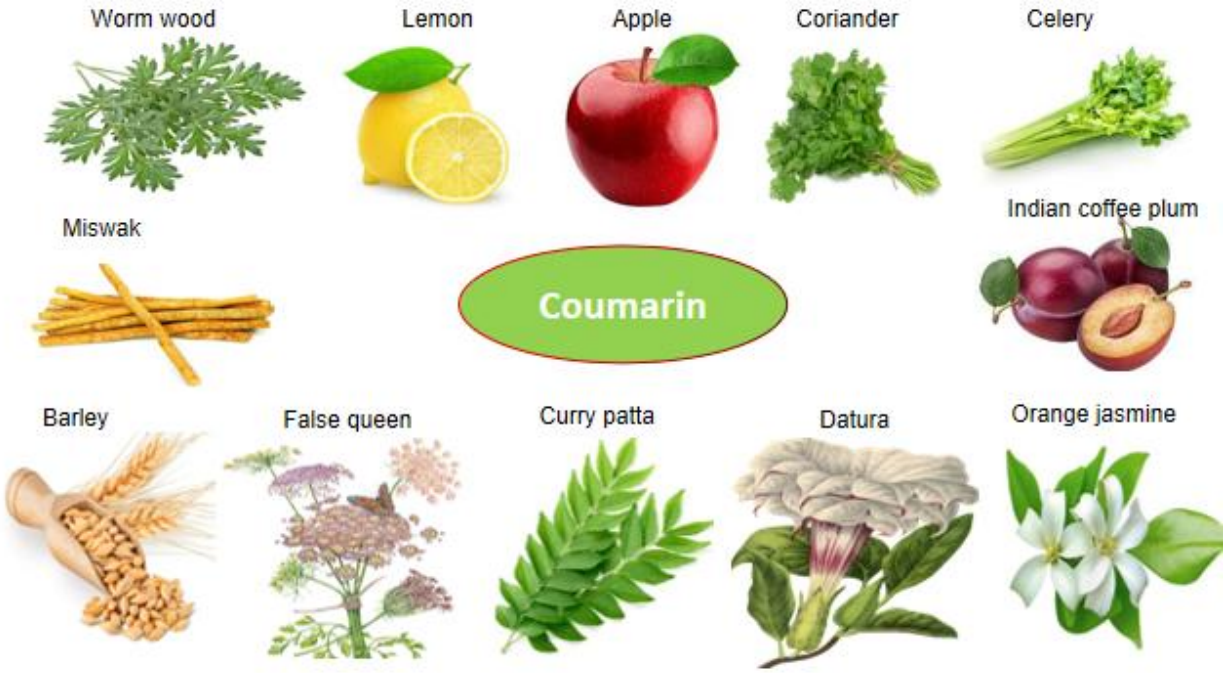


Table.1: ***In this table some plants are given which are source of coumarin***

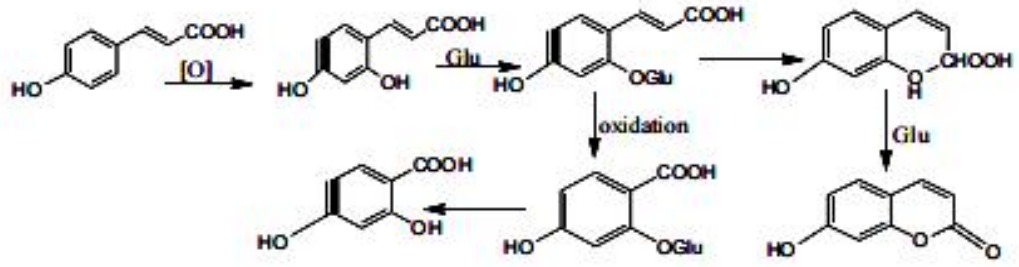
S.No	Plant name	Scientific name	Mode of action	References
1	Golden Apple	Aegle marmelos	Work by lowering nuclear factor kappa	(Murthy et al., 2019)
2	Citron ,rough lemon	Citrus medica	Works via estrogen receptor	(Wang et al., 2023)
3	Curry patta	Murrya koenigii	Works by down regulation of PGE2	National center for biotechnology info(2022)
4	Meetha neem	Murrya paniculata		// // // //
5	Himalayan Stellera	Stellera chamaejamse	Induce expression of anti-inflammatory cytokines	(Liu et al., 2016)
6	Orange berry and gin berry	Glycosmis pentaphylla		Scopolin 2022 and (Pan et al., 2009)
7	Blessed thistle	Silbum marianum	Work by reducing proinflammatory cytokines	(Murrya and paniculata 2022)

8	Orange jasmine	Murrya paniculata	Reducing oxidative stress	// // //
9	Turmeric	Curcuma zedoaria	Inhibiting writhing and nociception	(Forest and climate change 2022) Gurib-fakim and Brendler (2004)
10	Indian coffe plum	Flacourtia jangomas	By suppressing NF-kB activation	(Aesar 2022)
11	Barley	Hordem spontaneum		(Wang et al., 2015)
12	False queen	Ammi majus	Inhibiting the pro inflammatory cytokines	(Elgamal et al., 2023)
13	Coriander	Coriandrum sativum	Suppressing genes involved inflammatory actions	(Selim et al., 2012)
14	Datura	Datura metel	By inhibiting the pro inflammatory cytokines	(Deng et al., 2022)
15	Worm wood	Artemisia absinthium	Suppressing the NF-kB signalling pathway	(Scoparone 2022) (Deng et al.,2019)
16	Thale cress,mouse earor arabidopis	Arabidopsis thaliana	Works by suppressing the NF-KB signalling inflammatory pathway	Scopolin,2022 (Pan et al., 2009)
17	Toothbrush tree/ miswak	Sativum salvadora persica	Suppressing and downregulation certain genes involved in inflammatory pathways	Fraxinol,2022 and (Selim et al., 2012)
18	celery	Apium graveolens	Works by reducing pro inflammatory and inflammatory cytokines	National centerfor biotechnology information;2004 and (jac et al.,2006)
19	kuruntu	Pamburus	Works by suppressing iNOS and COX-2 protien expression	India biodiversity portal, 2022 and (Tuan et al., 2017)
20	Indian paper plant/tree	Daphne papyracea	Suppressing activitation of macrophages	(Liu et al., 2016)

4. Biosynthesis of Coumarin:

The higher plants are mostly associated with the production of coumarin. On the other hand, it was also discovered that a number of microbes, including bacteria and fungus, may manufacture coumarin molecules via certain metabolic pathways (Costa et

al., 2016). Simple coumarins are biogenetically produced from shikimic acid, via cinnamic acid. The specificity of the process is the C-2 hydroxylation, producing a break (β-oxidation) of the side chain (i.e. *Salix* spp.), or chain isomerization and subsequent lactonization, generating the umbelliferone. Figure 5 explains the entire process (Dewick 2002).



Salicylic acid **Umbelliferone**

Fig. 5: Biosynthesis of simple coumarins.

Pyrano and furocoumarins are also biogenetically produced from shikimic acid. These coumarins could be divided in two groups—lineal and angular—depending on the position where the isopentenyl pyrophosphate is condensed to further cyclize and form the heterocycle (Bruneton 1993).

5. Bioavailabilty of coumarins:

Bio availability is described as "the extent and rate to which the active drug ingredient or active moiety from the drug product is absorbed and becomes available at the site of drug action." Generally speaking, bio availability refers to a compound's absorption from the gastrointestinal tract when a dose form is taken orally (Chow 2014 , Dalton and Yates 2007).

The more crucial question is how much of the substance is bioavailable; knowing the amount of the compound(s) consumed is thus not sufficient. Compound concentrations, however, are often not immediately determinable at the site of action. Because of this, a lot of bioavailability tests focus on figuring out how much of the active ingredient is in the blood or urine.Thus, bio availability is involved with how fast and how much of a compound appears in the blood after a specific dose is administered.

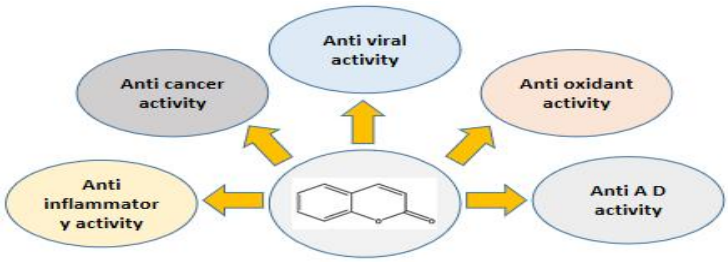
A pharmacokinetic study was carried out by Ritschel and Hoffmann who have compared between prolonged release of coumarin containing tablets with intravenous and per oral administration of coumarin solution in humans, where a correlation was established between the percent of drugs released in vitro and the area under the curve (AUC).

According to a research, rats treated with a coumarin-based prodrug system had four times higher oral bioavailability than rats treated with meptazinol (Xia et al., 2005). In another kinetic study, Abraham et al., 2011 presented that the absorption of coumarin from cinnamon powder is slightly lower than that of isolated coumarin.

In another research,With sertraline, an antidepressant medication the replacement of a chloride anion by coumarin-3-carboxylate increases the original drug's pharmacological effectiveness by binding to bovine serum albumin more strongly while maintaining the antibacterial qualities of the antidepressant molecule (Escudero et al., 2016). In order to increase paclitaxel's bioavailability, newly developed coumarins can be suppressed for P-gp-mediated efflux inhibition. Additionally, they can inhibit the growth of breast cancer stem cells, which is essential for developing powerful anticancer medications (Tripathi and Misra 2016).

There are very few studies on the bioavailability of coumarins. Therefore, future pharmacological studies are needed to study the bioavailability of naturally pharmacologically active coumarins.

6. Activities of Coumarin

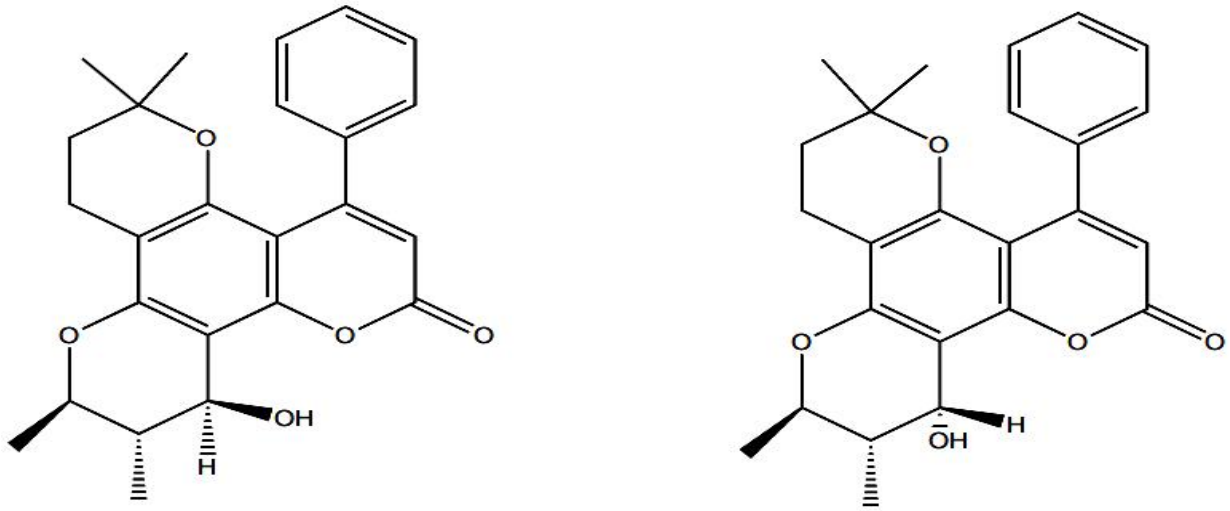


6.1 Antioxidant Activity

A coumarin derivative called fraxin shows antioxidant activity in an in vitro model where cells stimulated with H2O2-mediated OS exhibit a protective scavenging response against free radicals at a high dose of 0.5 mM (whang et al., 2005). Escletin (6,7-dihydroxycoumarin) was another coumarin that showed antioxidant properties by preventing H2O2-induced fibroblast damage in an in vitro model using Chinese Hamster lung cells (V79-4) (kim et al., 2008). The pyranocoumarins grandivitin, agasilin and aegelinol benzoate isolated from the roots of *Ferulago campestris* (Apiaceae), showed an antioxidant effect by examin the effect on human whole blood leukocytes and on isolated polymorphonuclear cells by chemiluminescence (Basile et al., 2009).

6.2 Antiviral activity

Many derivatives of natural origion have shown antiviral activities, including the coumarins, but the antiviral therapeutic effect depends on the substituent. Some of these derivatives have been tested against HIV (Kashman et al., 1992). In the same way, new coumarin derivatives such as inophyllumsand calanolides isolatedfrom the gaint African snail *Achatina fulica* have shown antiviral effect. Inophyllums B and P inhibited reverse transcriptase (RT) in HIV cell culture, selectively against HIV-1 (Patil et al., 1993).



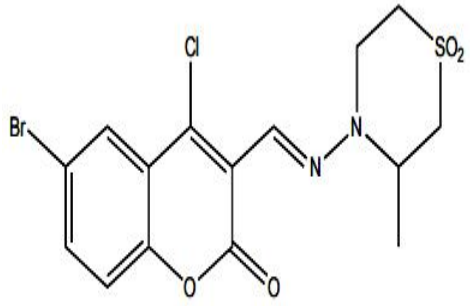
A B

Fig.6: hemical structure of inophillums B (A) and inophillums P (B).

6.3 Anticancer Activity

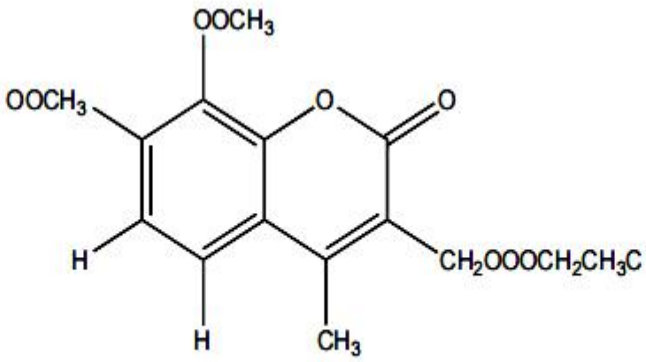
Malignancies have become the biggest threat to human health. The primary characteristic of coumarins that appears to be most significant is their anticancer activity, however the specifics of each interaction mechanism are yet unclear. A synthetic coumarin derivative (RKS262) (fig A) may inhibit the growth of ovarian cancer cells. This substance reduced the potential for mitochondrial transmembrane depolarization, controlled the mitochondrial Bcl-2 family pathway, increased the expression of the pro-apoptotic factors Bid, Bad, and

Box and decreased the expression of Bcl-xl and Mcl-1 (Singh et al., 2011). This process has been validated by a newly created dicoumarin polysulfides called SV25 (fig F), which stopped HCT116 colorectal cancer cells in the G2/M phase of the cell cycle, increased the level of bax and cytochrome c, and cleaved caspase 3 and caspase 7 (Saidu et al., 2012). Recent study shows coumarin derivatives Tr1 and Tr2 (Fig. C and D) can interact with the G-quadruplex and stabilize it (Raju et al., 2014). This amazing discovery showed a new target of cancer treatment. Furthermore, another coumarin 7-Diethyl amino-3(2 0-benzoxazolyl)-coumarin (DBC), exhibits its anticancer effects by inhibiting the microtubule and arresting the tumor cells at G2/M stage and its damage to human normal fibroblast is less than to the tumor cells (Kim et al., 2009). Colorectal carcinoma is the most common cancer in Western Europe and North America countries. 5,7-dihydroxy-4-methyl-6-(3-methylbutanoyl)- coumarin (DMAC，Fig. B) designed by Cheng-Wei Lin group can inhibit the colon cancer cell HCT116 and LoVo cells, the results demonstrating that the substance DMAC induce cell apoptosis by increasing the expression of proapoptotic protein Bak and activating the splitd caspase-3 and PARP, additionally, the DMAC induced celluar shrinkage, chromatin condensation and annxin V detection (Lin et al., 2014).



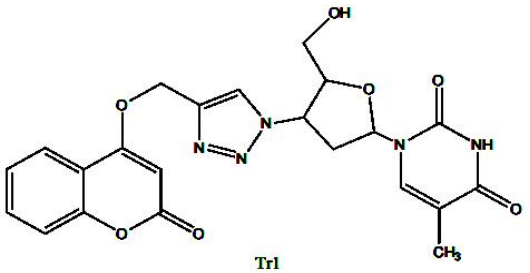
RKS262

A

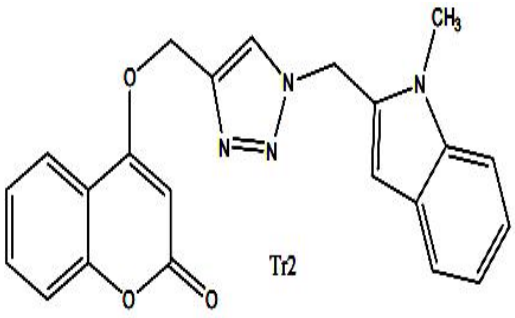


DAEMC

B

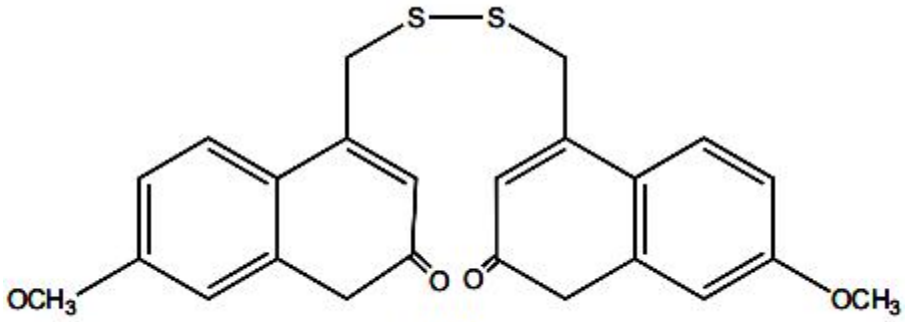


Tr1



Tr2

D



E SV25

6.4 Anti Inflammatory Activity

The inflammatory process is the response to an injurious stimulus. It can be evoked by a wide variety of noxious agents (*e.g.*, infections, antibodies, or physical injuries). The ability to mount an inflammatory response is important for survival in the face of environmental pathogens and injury. In some conditions and diseases, the inflammatory response may be exaggerated and sustained without apparent benefit and even with severe negtive effects. Warmth, discomfort, redness and swelling are all common signs of inflammation, regardless of what caused it. It has been described that some, but not all, NSAIDs may interfere with adhesion by inhibiting expression or activity of certain of these cell-adhesion molecules. Although they are actively being developed, new classes of anti-inflammatory medications that target cell adhesion molecules have not yet reached the clinical stage. Coumarin and their derivatives are very effective against inflammatory response (Goodman & Gilman's 2006).

Table 2 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 are also mentioned in the table 2 in brief. (Sharifi et al., 2021).

Table.2: ***Work Of Coumarins As An Anti-Inflammatory Compound Is Given In The Table***

S. NO	Coumarin compound	Formula	Plant(common names)	Scientific names	Mode of anti-inflammatory action	references
1	Scopoletin	C10H8O4	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	(Han et al., 2015) (Ding et al., 2008) (Chang et al., 2012) (Debago et al., 2009)
2	Scoparone	C11H10O4	Virgate worm wood, Worm wood	*Artemisia scoparia*, *Artemisia absinthium*	Works primarily by suppressing the NF-κB signalling	(Scoparone 2022) (Abisthinum 2022) (Lu et al., 2018)

					inflammatory pathway	(Liu et al., 2019)
3	Fraxetin	C10H8O5	Datura or trumpet flower	*Datura stramonium*	Works by suppressing pro inflammatory cytokines induced NF-κB signalling inflammatory pathway	(Fraxetin 2022) (Li et al., 2012) (Whang et al., 2020) (Dheng et al., 2022)
4	Fraxinol	C11H10O5	Prostrate cherry, mountain cherry, Rock Cherry, Creeping Cherry, Spreading Cherry	*Prunus prostrata*	Works by by inhibiting T-cells and prostaglandin biosynthesis	(NCBI 2022) (Mountain flowers of India 2022) (Soto-Balanco 2022)
5	Umbelliferone	C9H6O3	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-Kb	(NCBI 2022) (Sim et al., 2015) (Wang et al., 2019) (Selim et al., 2012)
6	6-hydroxy-7-methoxy-4 methyl coumarin	C11H10O4	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	(NCBI 2004) (Haggar et al., 2015) (Quattrocchi 2012) (Walliser 2014)
7	4-methyl-umbelliferone	C10H8O3	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	(Duddeck et al., 2013) (NCBI 2004) (Yamazaki and Tokiwa 2010)

8	Isofraxidin	C11H10O5	Celery	*Apium graveolens*	Works by reducing pro inflmmatory cytokines and by attenuating the increased expression of inflammatory enzymes	(Jin et al., 2018) (Jacqueline 2006) (Yamazaki and Tokiwa 2010)
9	Esculin	C15H16O9	Barley	*Hordeum spontaneum*	Reported to work by reducing proinflammatory and inflammatory cytokines	(NCBI 2004) (Wang et al., 2015) (GRIN 2022)
10	Scopolin Murrayin	C16H18O9	Thale cress, mouse-ear cress or Arabidopsis, Mugwort, wormwood,	*Arabidopsis Thaliana,* *Artemisia minor*	Reported to work by reducing proinflammatory and inflammatory cytokines	(Scopolin 2022) (Rutten et al., 2018) (EFlora of India 2022) (Whiffen et al., 2022)

6.5 Alzheimer's Disease Inhibition Activity

Alzheimer's disease (AD) is the degenerative disease of the central nervous system characterized by memory impairment, cognitive dysfunction, personality change and language barrier (Anand et al., 2011). In older people, AD is the most common disease and the number of people who effected from AD is rapidly increased. However, the causes of AD are well known, many researches show that low levels of acetylcholine (ACh), amyloid-β (Aβ) formations and oxidative stress appeared in patients (Mckhann et al., 2011 and Huang et al., 2014). Previous researches showed that coumarin derivatives can inhibit the AD. Maria Joao Matos group designed and produced a series of 3-substituted coumarin derivatives, for which the results of biology evaluation described that these compounds can both inhibit the MAO-A (Monoamine oxidase A) and MAO-B (Monoamine oxidase B) isoforms and AChE (acetylcholinesterase) in the micromolar range. A series of tacrine-coumarin hybrids designed and synthesized by Xiao-Bing Wang group showed a significant ability against AD by inhibiting the cholinesterase (ChE) and inducing β-amyloid (Aβ) aggregation, a substance which shows the best activity IC50 = 0.092 μM for inhibiting AChE, also showing a great ability to inhibiting butyrylcholinesterase (BuChE) whth IC50 = 0.234 μM; furthermore, the compound displays its activity by binding and activating the AChE peripheral and midgorge sites (Xie et al., 2013).

7. Uses of Coumarin

Coumarins are used in the food, cosmetic, and perfume industries, as well as in the pharmaceutical

sector where they are synthesized into several synthetic medicines (Annunziata et al., 2020).

It can also be used as a fixative and to boost the scent of essential oils in goods like toothpaste, hair preparations, toilet cleansers and perfumes. It can also be added to tobacco products to improve and fix their natural flavor and aroma (Fesser and Ellis 1974).

The use of coumarin in clinical medicine was suggested because of its biochemical characteristics. It had been tested for a number of clinical conditions, leading to the use of different dosage schedules. Doses of 8 mg for treating venous constriction and 7000 mg per day for anti-neoplastic therapies are recommended (Lacy and Kennedy 2004).

Fig.7: Some drugs made up of coumarin

Unlike synthetic pharmaceutical formulations and chemicals, natural coumarin substances are derived from plant sources and hence have little or no negative effects. These natural compounds can be used in combination with other pharmaceutical combinations. According to studies, the majority of coumarin compounds have antioxidant and anti-inflammatory properties. Hence, this makes these natural bioactive coumarins a perfect and potent candidate for developing potential anti-inflammatory drug formulations with dual benefits (Debosree et al., 2012).

Coumarins have cytotoxic and cytostatic effects against Hep2 cells and they have the ability to inhibit proliferation in lung (A549, H727), renal (ACHN), breast (MCF7) and leukemia (HL-60) cancer cell lines, showing inhibition effects on cell cycle phases, nuclear fragmentation, cell membrane loss and even inducing apoptosis (Benci et al., 2012 and Mirunalini et al., 2014).

The biological characteristics of coumarins are very interesting. Both coumarin and coumarin derivatives has been shown that 4-hydroxycoumarin and 7-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell line (Budzisz et al., 2003).

Furthermore, coumarins are widely used as laser dyes, insecticides, and optical brighteners (Aslam et al., 2010).

Additionaly, coumarins have an crucial role in plant biochemistry and physiology, acting as antioxidants, antifungal, enzyme inhibitors and precursors of toxic substances and also used in treating skin diseases, asthma and lymphedema (Šarkanj et al., 2013 and Önder 2020).

8. Conclusions

According to many studies, coumarins are very attractive substances. The origin, natural sources, biosynthesis, chemical profile, bioavailability and applications were also described. An explanation of the chemical profile, bioavailability, biosynthesis, origin, natural sources and applications was provided. This research highlighted and analyzed the role of coumarins as significant phytochemicals and their interesting uses.Coumarins have been increasingly attracting special interest as phytochemicals due to their underlying outstanding contributions in the prevention and treatment of diseases.A broad class of phytochemicals found in many foods consumed by humans are coumarins. Several of the therapeutic applications of plant extracts containing coumarins have been demonstrated in experimental models, indicating that the extracts have a range of pharmacological activities. The anti-inflammatory, anti viral, antioxidant, antitumor and other pharmaceutical properties make the coumarins as important class for therapeutic applications. In

order to fully explore and utilize the potential of coumarins, we hope that this review will help.

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