Review article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

A Comprehensive Review on Anti-inflammatory Activity of Coumarins

Chattopadhyay Kumar Sudip*

Santipur College, Santipur–741404, Nadia,West Bengal, India
E-mail: s.k.chattopadhyay@gmail.com

ABSTRACT

Among the different biologically important heterocycles coumarin and its derivative are the most versatile due to their various applications in various fields. The wide spectrum of biological activities such as antimicrobial, anti-inflammatory, anti-HIV, anticancer etc. has motivated the researchers to search for new variety with better activities. The modified coumarin derivatives specially the coumarin hybrids have established themselves as better alternatives for the treatment of several incurable diseases. Since inflammation is very much related to several diseases, there is always a continuous search for new anti-inflammatory agents, which can exhibit better activity and lower side effects than the known non steroidal anti-inflammatory drugs (NSAID). Numerous naturally occurring and chemically synthesized coumarins have exhibited therapeutic potentiality as ani-inflammatory agent. This review article provides recent updates of anti-inflammatory activities of naturally occuring and chemically synthesized coumarin derivatives.

KEYWORDS: Coumarins, anti-inflammatory activity, NSAID, cyclooxygenase.

***Corresponding author**

Sudip Kumar Chattopadhyay

Department of Chemistry

Santipur College,Santipur–741404, Nadia,West Bengal, India.

E-mail: s.k.chattopadhyay@gmail.com

INTRODUCTION:

Inflammation can be defined as the complex array of protective responses of the tissues to the injury which may vary from local to systemetic. The inflammatory responses are characterised by the accumulation of fluids and leukocytes. The important symptoms of inflammation are redness, swelling, generation of heat, loss of function of organs and pain which is the classic symptom of inflammation.[1] These all symptoms have resulted due to different cellular process such as vasodilatation which occurs due to changes in fluidity of blood caused by changes in smooth muscle cell function, increase in vascular permeability, localisation of phagocytic leukocytes at the site of inflammation and phagocytosis. Therefore an urgent need is to control the inflammation to protect the body function. In recent decades, the research activities to understand the mechanism of inflammatory process have been increased due to several new findings from the biochemical, molecular and functional animal models along with the clinical studies. This understanding plays the pivotal role for the development of new compounds with therapeutic potentiality in the treatment of several inflammation related diseases like rheumatoid arthritis, asthma, inflammatory bowl diseases, cancer, cardiovascular diseases and others. In the treatment of various types of inflammation, wide usages of non steroidal antiinflamatory drugs (NSAID) like Ibuprofen, Piroxicam, Etoricoxib etc. (Figure 1) are frequently administered. However different side effects like ulcers, haemorrhages, schizophrenia, heart attack and even stroke associated with all the NSAIDs limit their clinical applications. Therefore efforts have been given in the search of NSAID devoid of all these side effects. Over several decades natural products have exhibited their potentiality as therapeutic drugs for the treatment of different diseases.[2,3] Among them, the most important and versatile is coumarin and its derivative for their wide spectrum of pharmacological activities.

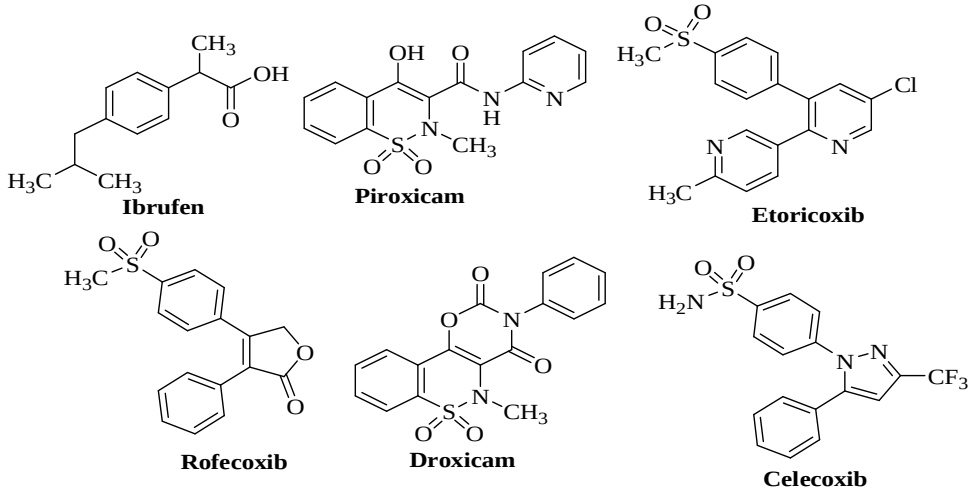

Figure 1: Representative examples of commercially available Non Steroidal Anti-Inflammatory Drugs (NSAID)

Coumarin is one of the most important members of benzopyrone family and its parent scaffold comprises of a benzene ring and □-pyrone ring fused with each other. The parent compound coumarin was first discovered and isolated from tonka bean (*Diptelyx odorata* Willd) in 1820 by Vogel and pharmacological activities of it were identified a century later.[4] Since, its first discovery, about 1300 coumarin compounds have been isolated as secondary metabolites from different plants, bacteria, fungi and also from animal sources.[5,6] The unique structural feature of coumarins is presumably responsible for wide applicability in both synthetic chemistry and biological field. Naturally occurring coumarin compounds have been observed to possess extensive biological activities such as antimicrobial, anti-inflammatory, anticancer, anti-HIV etc. and a few of them are being used as commercially available drugs (Figure 2). These extensive and versatile pharmacological activities of natural coumarin have motivated researchers to synthesize several modified coumarin hybrids with potential biological activities.

The potentiality of natural and synthetic coumarins as anti-inflammatory agent has been well researched and established. The different side effects of the clinically established market available non steroidal anti-inflammatory drugs (NSAID) have raised the prospect of coumarin compounds to replace these NSAIDs for better activity and poor side effects. Numerous research articles have been published to uncover the anti-inflammatory activities of coumarin derivatives. In this review an effort has been given to cover the anti-inflammatory activities of different natural and recently developed synthetic coumarins.

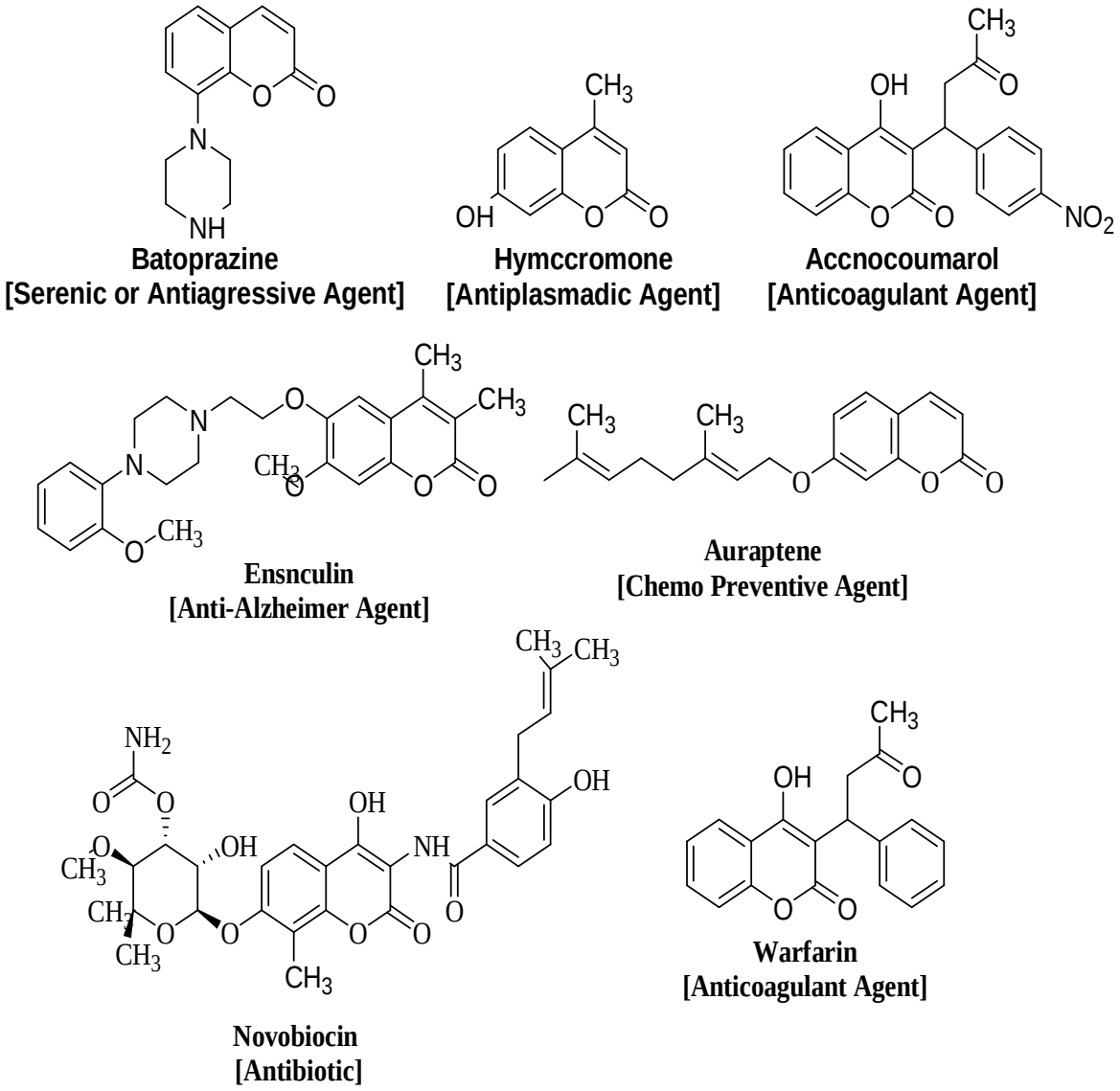

Figure 2: Examples of medicinally important coumarin compounds used as drugs

2. NATURAL COUMARINS AS ANTI-INFLAMMATORY AGENTS:

Wide varieties of naturally occurring counmarins have demonstrated the inhibitory activity against inflammation in various diseases. For simplicity, the anti-inflammatory activity of naturally occurring coumarins has been sub-classified according to their chemical structures: simple coumarins and heterocycle fused coumarins.

2.1 *Anti-inflammatory activity of simple coumarins*:

A number of simple coumarins with substituents like hydroxyl, methoxyl, phenyl, prenyl group and even long chain as substituent mainly at C-4, 6, 7 and 8 positions including coumarin

itself have shown anti-inflammatory activity (Figure 3 and 4). Piller, in 1975, once reported that simple coumarin **1** itself or in combination with sodium-rutin-sulphate marketed as Venolot, exhibits the potentiality to act as anti-inflammatory agent by stimulating phagocytosis, enzyme production and thus proteolysis along with subsequent removal of protein and oedema fluid from the injured tissues.[7]

Substituted coumarin, for example, esculetin **2** isolated from from *Cichorium intybus* [8] and *Bougainvillea spectabilis* Wild (Nyctaginaceae)[9] is naturally occurring simple coumarin with two hydroxyl group at the C-6 and C-7 positions of the benzene ring of the coumarin scaffold. This phenolic nature of esculetin makes it very much suitable to act as anti-inflammatory agents. An investigation of the effects of esculetin in an experimental model of rat colitis induced by trinitrobenzenesulphonic acid (TNBS) was reported by Stasi *et al*.[10] They showed that in the acute colitis model, esculetin promotes a reduction in the extension of the lesion which is accompanied by a decrease in the occurrence of diarrhoea with the restoration of the glutathione content. Plant derived scopoletin (6-methoxy-7-hydroxycoumarin) **3**, scoparone (6,7-dimethoxy-coumarin) **4**, fraxetin (7,8-dihydroxy-6-methoxycoumarin) **5**, 4-methylumbelliferone (4-methyl-7-hydroxycoumarin) **6**, esculin (6,7-dihydroxy-6-O-glucosylcoumarin) **7**, daphnetin (7,8-dihydroxycoumarin) **8** are active against intestinal inflammatory process induced by TNBS in rats at doses of 5, 10 or 25 mg/kg and can be considered as anti-inflammatory agent at active doses.[11] Scopoletin **3** was also isolated from *Hypochaeris radicata*.[12]

Isofraxidin **9**, a coumarin compound isolated from *Sarcandra glabra* (Thunb.)[13] and the stem bark of *Acanthopanax senticosus* [14] has also been found to exhibit anti-inflammatory activities through the regulation of pro-inflammatory cytokines, TNF-α and the phosphorylation of p38 and ERK1/2. A significant inhibitory effect on the cell growth in the human synovial sarcoma cell line, SW982 was also exhibited by isofraxidin.[14] Further, murracarpin **10** from *Murraya paniculata* leaves is a simple coumarin compound and showed strong anti-inflammatory activity presumably due to the presence of a methoxyl group at C-7 position and a homoallylic short chain at C-8 position with methoxyl group at the homoallylic position and an hydroxyl group at the allylic position of this short chain.[15]

The evaluation of anti-inflammatory activity of two structurally similar coumarin compounds, aculeatin **11** and toddaculin **12** isolated from *Toddalia asiatica* (L.) LAM., using lipopolysaccharide (LPS)-stimulated RAW264 mouse macrophage cells have resulted a significant inhibitory activity against mRNA expression of inflammatory mediators and nitric oxide production.[16] Further, cellular uptake has pointed towards the decrease in hydrophobicity of a

molecule involving in the mechanisms of anti-inflammatory activity might be due to the epoxidation of the prenyl group.

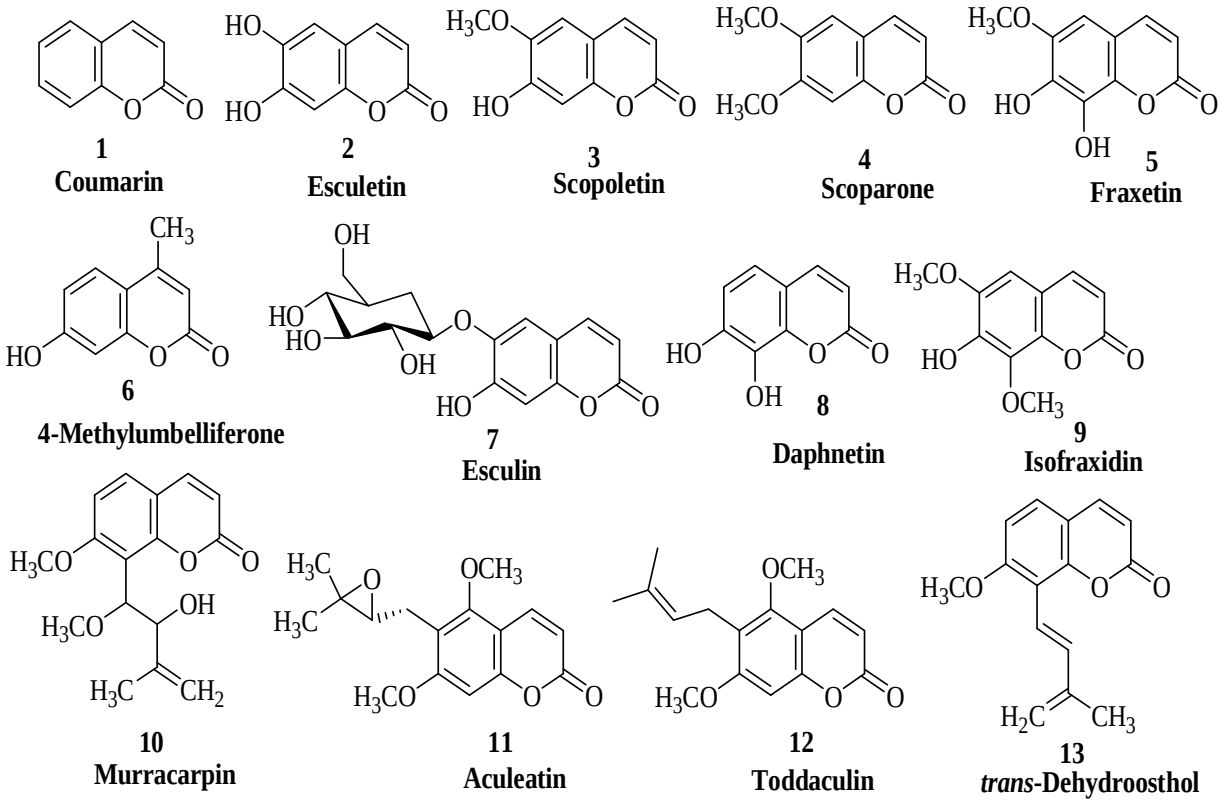

Figure 3: Different anti-inflammatory active naturally occuring simple coumarins

Among the different coumarins isolated from the roots of *Murraya exotica*, trans-dehydroosthol **13**, sibirinol **14**, and cis-osthenon **15** demonstrated anti-inflammatory activity. These compounds showed inhibition against LPS-induced NO production in BV-2 microglial cells.[17]

The *in vitro* anti-inflammatory activity of 5,7,4′-trimethoxy-4-phenylcoumarin **16** and 5,7-dimethoxy-4-phenylcoumarin **17** obtained from *Streptomyces aureofaciens* CMUAc130 was demonstrated by Taechowisan and co-worker. The investigations carried out on the formation of NO, PGE2, and TNF-α along with on inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-induced murine macrophage RAW 264.7 cells revealed significant inhibitory effect against the formation of TNF-α.[18,19]

Several significant researches on osthole **18**, an important naturally occurring coumarin has revealed its efficacy as anti-inflammatory agent.[20,21,22,23] For example, Ka and co-worker established the potentiality of osthole as renoprotective compound for focal segmental glomerulosclerosis (FSGS), a common chronic kidney disease by the decrease in NF-κB activation, COX-2 expression

as well as PGE2 production, podocyte injury and apoptosis.[24] In another report Wu *et al.* described the ability of osthole as anti-inflammatory agent by the decrease in pro-inflammatory cytokine and mediator production *via* suppression of the NF-κB and MAPK signalling pathways in HepG2 cells when they were incubated on the differentiated medium from 3T3-L1 cells.[25]

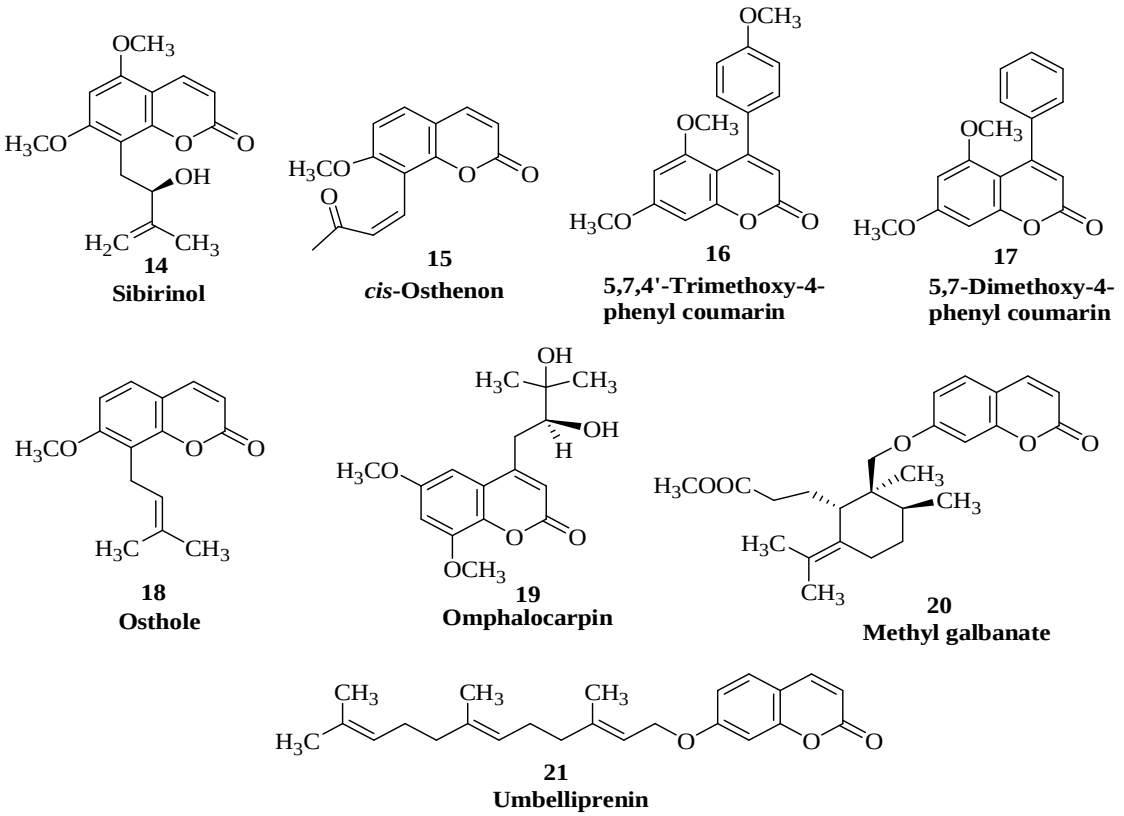

Figure 4: Different anti-inflammatory active naturally occuring simple coumarins

An *in vitro* and *in vivo* examination of anti-inflammatory activity of omphalocarpin **19**, a prenylcoumarin isolated from *Radix Toddaliae* Asiaticae, was reported by Zhang and co-worker.[26] The anti-inflammatory mechanism of omphalocarpin might be attributed to the inhibition of pro-inflammatory mediators including nitric oxide, IL-6 and TNF-α. They also reported that omphalocarpin reduced the overproduction of NO through down-regulation of the expression and enzymatic activity of iNOS and COX-2 in LPS-stimulated macrophage, which was due to the suppression of NF-κB activation in the transcriptional level.

While studying the *in vitro* immunomodulatory and anti-inflammatory properties of terpenoid coumarins, methyl galbanate (MG) **20** and umbelliprenin (UMB) **21**, Mahmoudi and co-worker reported that these two compounds reduced the PHA-induced splenocyte proliferation and T_H2 IL-4 and thereby suppressed T_H1 IFNc.[27] They also reported that both these compounds suppressed

lipopolysaccharide (LPS)-induced generation of NO and PGE2 leading to reductions in inducible iNOS and COX- expression.

2.2 *Anti-inflammatory activity of heterocycle fused coumarins*:

Different linear and angular furano and pyrano coumarins have shown significant anti-inflammatory activities (Figure 5). Imperatorin **22**, a linear furano coumarin, isolated from different plants species, for example, the dried roots and rhizomes of *Glehnia littoralis* (Umbelliferae)[28] and from the plant *Radix Angelicae dahuricae* possess anti inflammatory activity.[29,30,31,32] In a recent report Wang *et al*. examined the anti-inflammatory effects of imperatorin in tumor necrosis factor-α (TNF-α)-stimulated HeLa cells by investigating its effect on the production and expression of cytokines and the major signal-transduction pathways.[33] They observed that imperatotrin could act as a potent inhibitor of NF-κB activation by the suppression of TNF-α-induced IKKα/β phosphorylation, IκB phosphorylation and degradation, and NF-κB p65 nuclear translocation. Therefore it could decrease inflammation by inhibiting the ROS-mediated activation of the PI3K/Akt/NF-κB pathway.

The dual cyclooxygenase-2 selective/5-lipoxygenase inhibitory activity of isoimperatorin **23**, a linear furano coumarin, isolated from the dried roots of *angelicae dahuricae*[34] have made it a good anti inflammatory agent for therapeutic purposes.[34,35] Rim and Cho *et al*. investigated the the anti-inflammatory activity of nodakenin **24**, a linear dihydrofurano coumarin, isolated from the roots of *Angelicae gigas*, by examining *in vitro* inhibitory effects on inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages and mouse peritoneal macrophages.[36] The *in vivo* effects of nodakenin on LPS-induced septic shock in mice was also examined. The results showed that nodakenin down-regulated the expression of the pro-inflammatory inducible nitric-oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β genes in macrophages by interfering with the activation of tumor necrosis factor receptor-associated factor 6 (TRAF6), thus preventing NF-κB activation.

Angular furano coumarin, columbianetin **25**, extracted from *Corydalis heterocarpa* with various solvents has demonstrated the anti-inflammatory effect by regulating mast cell-mediated allergic inflammatory responses.[37] In a recent report columbianetin have also been observed to exhibit anti-inflammatory effect on lipopolysaccharide stimulated human peripheral blood mononuclear cells.[38] Libanoridin **26**, another angular furano coumarin, also isolated from *Corydalis heterocarpa* exhibited its efficiency to act as anti-inflammatory agent by inhibiting the protein expression levels of inflammatory mediators such as inducible nitric oxide synthase (iNOS),

cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), and interleukin-1b (IL-1b) in a dose-dependent manner in LPS-stimulated HT-29 cells.[39]

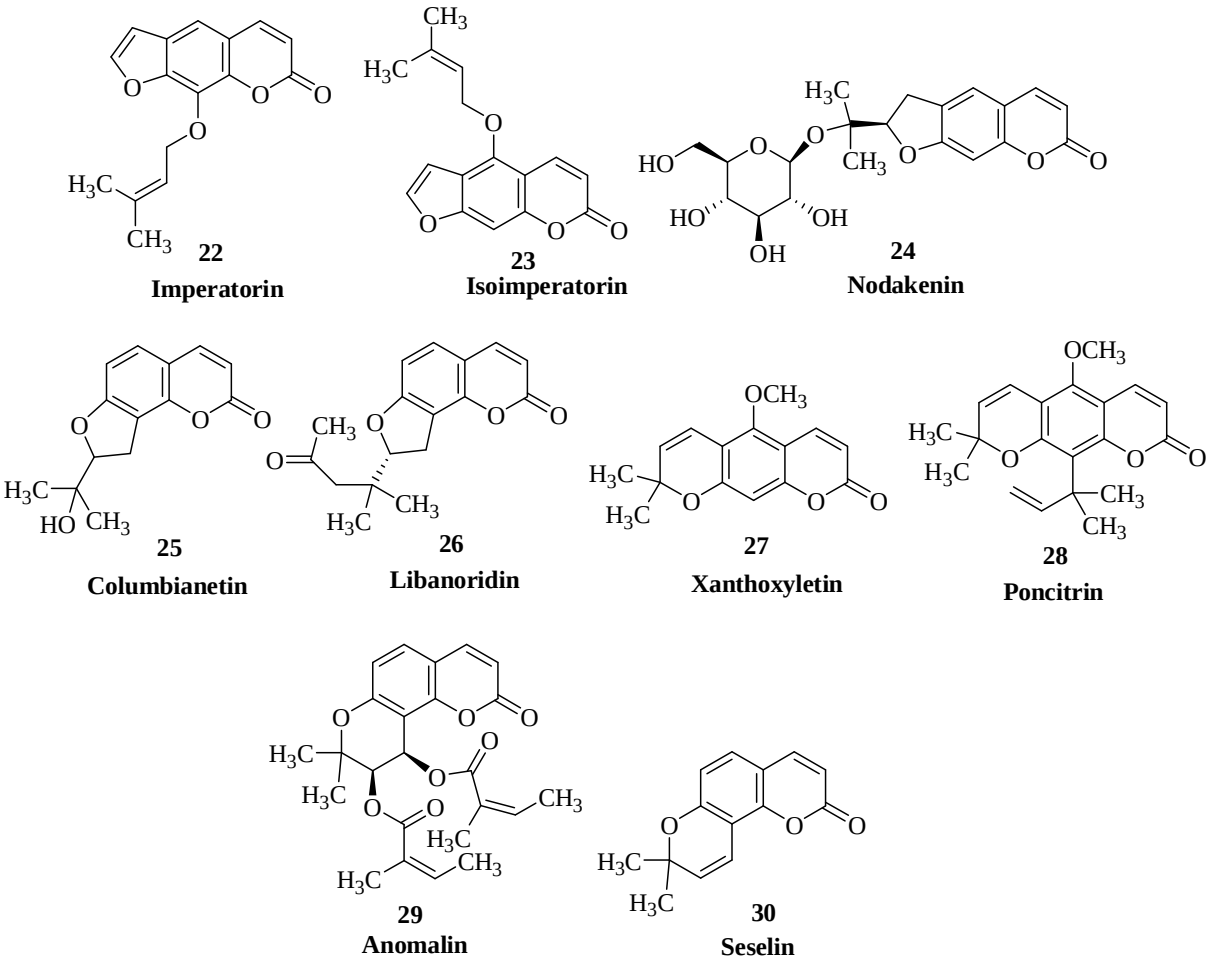

Figure 5: Naturally occuring heterocycle fused coumarins possessing anti-inflammatory activity

Naturally occurring linear pyrano coumarins have also been observed to exhibit anti-inflamatory activity. Nakamura *et al*. reported that xanthoxyletin **27** and poncitrin **28**, two linear pyrano coumarins isolated from *Clausena guillauminii* (Rutaceae), exhibited an inhibitory effect on iNOS protein expression.[40] The author also reported that xanthoxyletin not only inhibited the synthesis of nitric oxide (NO) but also the protein expression of tumor necrosis factor-alpha (TNF-α) and cyclooxygenase-2 (COX-2).

Angular coumarin like anomalin **29,** isolated from *S. divaricata*, was reported to exhibit anti-inflammatory activity in a dose dependent manner.[41] Anomalin inhibited inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) mRNA and protein expression in LPS-stimulated

RAW 264.7 macrophage. Tsai *et al*. demonstrated that angular pyrano coumarin, seselin **30**, isolated from *Plumbago zeylanica*, exhibited anti-inflammatory activity since it inhibited PBMC proliferation-activated with PHA with an IC_{50} of 53.87 ± 0.74 μM.[42] The action of seselin was assumed to involve the regulation of cell cycle progression, interleukin-2 (IL-2) and interferon (IFN) production in peripheral blood mononuclear cells (PBMC). The experimental investigations revealed that seselin not only stopped the cell cycle progression of activated PBMC from the G1 transition to the S phase but also suppressed IL-2 and IFN- production in a concentration-dependent manner.

3. SYNTHETIC COUMARINS AS ANTI-INFLAMMATORY AGENTS:

Since its first synthesis in 1882 numerous synthetic approaches for the construction of coumarin scaffold have been reported.[43] Of these gathering several newly synthesized compounds possess anti-inflammatory activity related to different diseases (Figure 6).[44] Rational design of theses molecule are based on the structure activity relationship of different naturally occuring cumarins. In addition hybridisation of coumarin with biologically active heterocyclic moieties has led to the development of numerous potent anti-inflammatory active agents.

Banerjee *et al.* reported a green synthetic route to access a variety of benzyl pyrazolyl coumarins **31** using neutral ionic liquid, [pmIm]Br as the reusable catalyst under metal-free conditions.[45] These compounds exhibited *in silico* binding affinity to COX-II inhibitor better than their individual moieties, 3-benzyl coumarins and pyrazolones. Further, 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-nitrophenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one showed even better binding affinity than the marketed anti-inflammatory drug, celecoxib.

Bansal *et al.* synthesized two series of novel coumarin derivatives by coupling coumarin and benzimidazole nuclei through different linkers.[46] These compounds were evaluated for anti-inflammatory and anthelmintic activities by *in silico* studies using PASS (prediction of activity spectra for substances) software. Among the different synthesized compounds, 4-[(Benzimidazol-2-yl)methyl]-7-methylcoumarin (**32a**) and 4-[(Benzimidazol-2-yl) methyl]coumarin (**32b**) exhibited maximum anti-inflammatory activity (45% inhibition), which is equivalent to the activity of indomethacin (48% inhibition) after 3 h (peak inflammatory response time).

A microwave assisted efficient, high-yielding and rapid synthesis of (*E*)-1,5-dimethyl-4-((2-((substituted-2-oxo-2H-chromen-4-yl)methoxy) naphthalen-1-yl)methyleneamino)-2-phenyl-1,2-dihydropyrazol-3-one derivatives **33** containing schiff base structures was described by Hosamani *et al.* [47] The anti-inflammatory activity of the synthesized compounds were evaluated by egg albumin denaturation method. The compounds **33a** and **33b** exhibited an inhibition of heat-induced protein

denaturation at the concentration (31.25 µg ml^{-1}) as 53.65% and 67.27%, respectively, and these compounds were more active than standard acectofenac drug (5.50%).

In another report Hosamani *et al*. described a rapid, expedient synthesis of novel coumarin-piperazine derivatives **33** in good yields.[48] The evaluation of *in vitro* anti-inflammatory activity of these synthesized compounds revealed that the compounds 4-((4-(4-Acetylpiperazin-1-yl)phenoxy)methyl)-6-methyl-3H-chromen-2-one (IC_{50} = 37.15 µg/mL) and 4-((4-(4-Acetylpiperazin-1-yl)phenoxy)methyl)-6-methoxy-3H-chromen-2-one (IC_{50} = 47.43 µg/mL) exhibited potent anti-inflammatory activity, which are comparable with the standard drug diclofenac sodium (IC_{50} = 30.45 µg/mL).

The anti-inflammatory potential of novel coumarin triazole hybrids **34** and **35**, synthesized by stepwise manner from orcinol were investigated against the pro-inflammatory cytokine, TNF-α on U937 cell line and compounds **34** (R = H and Br) and **35** (R = *t*Bu) were observed to exhibit promising anti-inflammatory activity.[49] Further investigation of these three compounds for their inhibitory effect on RANKL-induced osteoclastogenesis in RAW 264.7 cells by using tartrate resistant acid phosphatase (TRAP) staining assay at 10 μM demonstrated that compound **34** (R = Br) exhibited dose dependent inhibition of RANKL-induced osteoclastogenesis by suppression of the NF-κB pathway.

Shastri *et al*. developed a green and efficient protocol for the synthesis of a series of coumarin based pyrano[3,2-*c*]chromene derivatives **36** using multi-component reaction (MCR) approach.[50] The anti-inflammatory assay was screened against HRBC membrane stabilization method and all the compounds exhibited excellent anti-inflammatory activity. The same author also reported the synthesis and biological studies of different tri- and tetrasubstituted coumarin–imidazole hybrids **37**.[51] The anti-inflammatory activity of all compounds was screened against matrix metalloproteins, MMP-2 and MMP-9 and all the compounds exhibited promising anti inflammatory activities.

The synthesis and evaluation of anti-inflammatory activities of a series of 9-substituted-9,10-dihydrochromeno[8,7-e][1,3]oxazin-2(8H)-one derivatives was described by Tian and Quan *et al*.[52] Among the synthesized compounds, 9-(2-Chlorophenyl)-9,10-dihydrochromeno[8,7-e][1,3]oxazin-2(8H)-one **38** exhibited anti-inflammatory activity significantly as it could inhibit inflammatory responses *via* suppression of the NF-κB and MAPK signaling pathways.

Dawood *et al*. reported the synthesis and anti-inflammatory activities of two series of coumarin derivatives containing thiazoline **39** and thiazolidinone **40** moieties.[53] Most of the synthesized compounds exhibited high *in vivo* anti-inflammatory activity along with superior GI

safety profiles (0–7% ulceration) as compared to indomethacin and *in vitro* high affinity and selectivity toward the COX-2 isoenzyme, compared to the reference celecoxib with IC_{50} values ranging from 0.31 to 0.78 μM.

Wabli *et al*. reported the synthesis of a series of 6-(substituted benzylamino)-7-hydroxy-4-methyl-2H-chromen-2-ones **41**starting from the 6-amino-7-hydroxy-4-methyl-*2H*-chromen-2-one and assessed their anti-inflammatory activity using the carrageenan-induced hind paw edema method.[54] Compounds (R = NO_2, $N(CH_3)_2$, NH-CO-CH_3, 3-NO_2) exhibited significant ($p < 0.001$) reduction of rat paw edema volume after 1 h from the administration of the carrageenan compared to the reference drug, indomethacin where as compounds (R = NH-$COCH_3$, 3-OH, 4-OCH_3) showed the highest anti-inflammatory activity, surpassing indomethacin after 3 h with 44.05% and 38.10% inhibition, respectively.

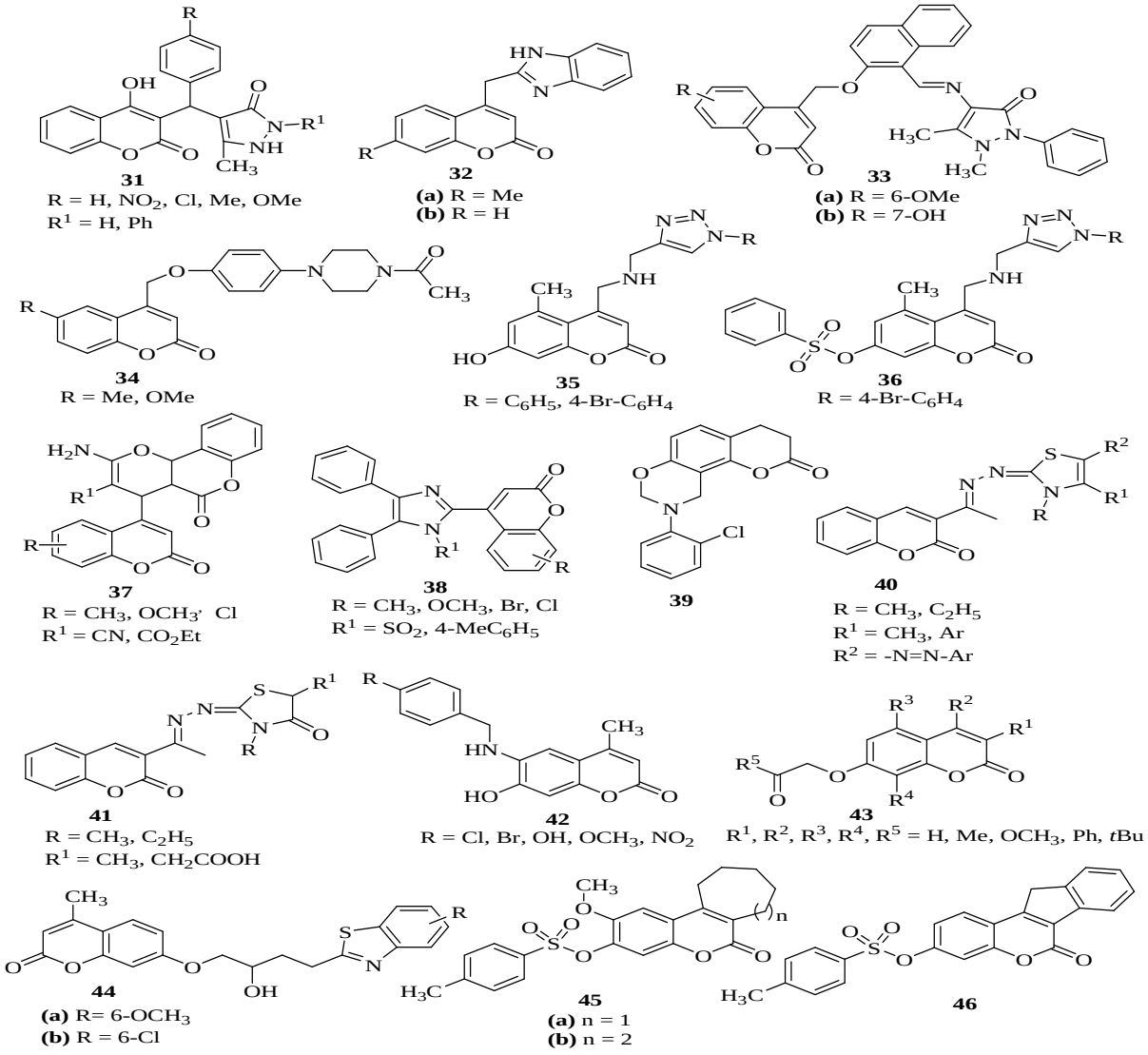

Figure 6: Synthetic coumarins as anti-inflammatory agent.

Jaenis *et al*. reported the synthesis of a series of 7-(2-oxoalkoxy)coumarins **42** by conjugating substituted 7-hydroxycoumarins with different chloroketones.[55] The anti-inflammatory properties of 7-(2-oxoalkoxy)coumarins were examined in LPS-induced inflammatory response in J774 macrophages. Among the synthesized compounds seventeen of them inhibited NO and IL-6 production over 50% at 100 μM concentrations whereas IC_{50} values of the best inhibitors were 21 μM/24 μM (NO/IL-6) and 30 μM/10 μM (NO/IL-6). The investigations revealed that the substitution with 7-(2-oxoalkoxy) group improved the anti-inflammatory properties of most of the investigated 7-hydroxycoumarins.

A number of 7-subsituted coumarin derivatives synthesized using various aromatic and heterocyclic amines were evaluated *in vivo* for anti-inflammatory and analgesic activity, and for ulcerogenic risk.[56] The *in vivo* anti-inflammatory and *in vitro* 5-LOX enzyme inhibition study showed that compounds **43a** (R = OCH_3) and **43b** (R = Cl)were the most potent compounds in all the screening protocols. The *in vitro* kinetic study of **43** showed mixed or non-competitive type of inhibition with 5-LOX enzyme. All the results, clearly pointed towards the presence of OCH_3 group in **43a** and Cl in **43b** at C6-position of benzothiazole ring, was found very important substitutions for their potent activity.

Lee *et al.* reported the synthesis and *in vitro* anti-inflammatory effects as inhibitors of lipopolysaccharide (LPS)-induced nitric oxide (NO) and prostaglandin E2 (PGE2) production in RAW 264.7 macrophages of a number of fused coumarin derivatives.[57] Compounds **45a** and **45b** were the most active PGE2 inhibitors with IC_{50} values of 0.89 and 0.95μM respectively since their effects were due to inhibition of both COX-2 protein expression and COX-2 enzyme activity as revealed by Western blot and cell-free COX-2 screening. In addition, the tetracyclic analog **46** were the most potent NO inhibitors, with IC_{50} value 53.59 μM.

4. CONCLUSION AND FUTURE PROSPECT:

The chemical structures of coumarins, particularly substituent and its nature, pattern of substitution and even number of substituent have shown profound effect on the pharmacological activities. In case of natural coumarins, the anti-inflammatory activity has been exhibited by compounds containing hydroxyl, methoxyl and prenyl group attached either with the benzene ring or with the pyrone ring. These structural features provide the underlying values for the future development of coumarin compounds with better anti-inflammatory activity, little drug resistances, poor side and good curative effects. This review article is an effort to cover the updated research activities carried out on coumarins with a focus on their anti-inflammatory activity. The comprehensive illustration of inhibitor potentiality of naturally occurring coumarins along with the

recently modified coumarin derivatives could assist researches in future to design compounds as anti-inflammatory agents. Despite all these efforts, further study on the elucidation of pharmacological mechanisms, the exploration of structure-activity relationships and the study of clinical applications are very much essential and this review article provides the researchers an expedient reference for the future development of novel anti-inflammatory drugs.

5. ACKNOWLEDGEMENT

The author is grateful to UGC and Santipur College for their assistance.

6. CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest

7. REFERENCES:

1. Levine JD, Reichling DB. Text Book of Pain: Peripheral mechanism of inflammatory pain. 4th ed. Churchil Livingstone: London; 1999: 59-84.
2. Calixto JB, Otuki MF, Santos ARS. Anti-inflamatory compounds of Plant Origin. Part I. Action on arachidonic acid pathway, nitric oxide and nuclear factor κ B (NF-κB). Planta Med. 2004; 69 (12): 93-103.
3. Calixto JB, Campos MM, Otuki MF, Santos ARS. Anti-inflamatory compounds of Plant Origin. Part II. Modulation of Pro-Inflammatory Cytokines, Chemokines and Adhesion Molecules. Planta Med. 2004; 70(3): 93-103.
4. Feuer G. The Metabolism and Biological Actions of Coumarins. Progress in Medicinal Chemistry, 1974; 10: 85-158.
5. Soine TO. Naturally Occurring Coumarins and Related Physiological Activities. Journal of Pharmaceutical Sciences. 1964; 53(3): 231-264.
6. Murray RDH, “The Naturally Occurring Coumarins”. In: Herz W, Falk H, Kirby GW, Moore RE (eds.) Progress in the Chemistry of Organic Natural Products. Springer: Verlag, Wien; 2002: 1-619.
7. Piller NB. A comparison of the effectiveness of some anti-inflammatory drugs on thermal oedema. British Journal of Experimental Pathology. 1975; 56(6): 554–560.
8. Nadkarni A, Nadkarni’s Indian Materia Medica. Popular Prakashan Pv. Ltd: Bombay, India; 1976;1
9. Chang WS, Chang YH, Lu FJ, Chiang HC. Inhibitory effects of phenolics on xanthine oxidase. Anticancer Research. 1994; 14(2A): 501–506.

10. Witaicenis A, Seito LN, Di Stasi LC, Intestinal anti-inflammatory activity of esculetin and 4-methylesculetin in the trinitrobenzenesulphonic acid model of rat colitis. Chemico-Biological Interactions. 2010; 186 (2): 211–218.
11. Witaicenis A, Seito LN, Chagas AdaS, Almeida Junior LD de, Luchini AC, Rodrigues-Orsi P, Cestari SH, Di Stasi LC. Phytomedicine. 2014; 21(3): 240–246
12. Senguttuvan J, Krishnamoorthy K, Subramaniam P, Krishnaswamy T, Subramanium K, Rajendran V. Confertin and scopoletin from leaf and root extracts of *Hypochaeris radicata* have anti-inflammatory and antioxidant activities. Ind Crop Prod. 2015; 70: 221-230.
13. Niu X, Xing W, Li W, Fan T, Hu H, Li Y. Isofraxidin exhibited anti-inflammatory effects *in vivo* and inhibited TNF-α production in LPS-induced mouse peritoneal macrophages *in vitro via* the MAPK pathway. International Immunopharmacology. 2012; 14(2): 164–171.
14. Yamazaki T, Shimosaka S, Sasaki H, Matsumura T, Tukiyama T, Tokiwa T. (+)-Syringaresinol-di-O-beta-D-glucoside, a phenolic compound from Acanthopanax senticosus Harms, suppresses proinflammatory mediators in SW982 human synovial sarcoma cells by inhibiting activating protein-1 and/or nuclear factor-κB activities. Toxicology *in Vitro*. 2007; 21(8): 1530–1537.
15. Wu LH, Liu SW, Zeng J, Xu RA. Anti-inflammatory and analgesic activity of coumarins in *paniculata* leaf. Chin J Spectros Lab. 2011; 28 (06): 2999-3003.
16. Kumagai M, Watanabe A, Yoshida I, Mishima T, Nakamura M, Nishikawa K, Morimoto Y. Evaluation of Aculeatin and Toddaculin Isolated from *Toddalia asiatica* as Anti-inflammatory Agents in LPS-Stimulated RAW264 Macrophages. Biol Pharm Bull. 2018; 41(1): 132–137.
17. Liu B-Y, Zhang C, Zeng K-W, Li J, Guo X-Y, Zhao M-B, Tu P-F, Jiang Y. Anti-Inflammatory Prenylated Phenylpropenols and Coumarin Derivatives from *Murraya exotica* J Nat Prod. 2018; 81(1): 22−33.
18. Taechowisan T, Tuntiwachwuttikul P, Lu C, Shen Y, Lumyong S, Taylor WC. Anti-inflammatory Activity of 4-Arylcoumarins from Endophytic *Streptomyces aureofaciens* CMUAc130 in Murine Macrophage RAW 264.7 Cells. Immunol Invest. 2007; 36 (2): 203–211.
19. Taechowisan T, Lu C, Shen Y, Lumyong S. *In vitro* anti-inflammatory activity of 4-arylcoumarins from endophytic *Streptomyces aureofaciens* CMUAc130 in murine macrophage RAW 264.7 cells. Nat Prod Res. 2007; 21(12): 1104–1113.

20. Liu JH, Zschocke S, Reininger E, Bauer R. Inhibitory Effects of Angelica pubescens *f. biserrata* on 5-Lipoxygenase and Cyclooxygenase. Planta Med. 1998; 64(6): 525–529.
21. Li F, Gong Q, Wang L, Shi J. Osthole Attenuates Focal Inflammatory Reaction Following Permanent Middle Cerebral Artery Occlusion in Rats. Biol Pharm Bull. 2012; 35(10): 1686–1690.
22. Liao P-C, Chien S-C, Ho C-L, Wang EIC, Lee S-C, Kuo Y-H, Jeyashoke N, Chen J, Dong W-C, Chao LK, Hua K-F. Osthole Regulates Inflammatory Mediator Expression through Modulating NF-κB, Mitogen-Activated Protein Kinases, Protein Kinase C, and Reactive Oxygen Species. J Agric Food Chem. 2010; 58(10): 10445–10451.
23. Wei M, Mo S-L, Nabar NR, Chen Y, Zhang J-J, He Q-L, Zou X-N, Liu X-G, Sun L-B, Zhou S-F. Modification of Rat Model of Sciatica Induced by Lumber Disc Herniation and the Anti-Inflammatory Effect of Osthole Given by Epidural Catheterization. Pharmacology. 2012; 90 (5-6): 251–263.
24. Yang S-M, Chan Y-L, Chen A, Hua K-F, Chang J-M, Chen H-L, Tsai Y-J, Hsu Y-J, Chao LK, Feng-Ling Y, Wu S-H, Tsai Y-L, Wang Y-F, Tsai C-L, Ka S-M. Osthole improves an accelerated focal segmental glomerulosclerosis model in the early stage by activating the Nrf2 antioxidant pathway and subsequently inhibiting NF-κB-mediated COX-2 expression and apoptosis. Free Radic Biol Med. 2014; 73 (8): 260–269.
25. Wu S-J. Osthole Attenuates Inflammatory Responses and Regulates the Expression of Inflammatory Mediators in HepG2 Cells Grown in Differentiated Medium from 3T3-L1 Preadipocytes. J Med Food. 2015; 18 (9): 972–979.
26. Tong L, Chen T, Chen Z, Pi H, Ruan H, Wu J, Zhang P, Pi H, Ruan H, Wu J. Anti-inflammatory activity of omphalocarpin isolated from Radix *Toddaliae* Asiaticae. J. Ethnopharmacol. 2014; 155 (3): 1553–1560.
27. Zamani TRS, Iranshahi M, Mahmoudi M. *In vitro* anti-inflammatory and immunomodulatory properties of umbelliprenin and methyl galbanate. J Immunotoxicol. 2016; 13(2): 209–216.
28. Yuan Z, Tezuka Y, Fan W, Kadota S, Li X. Constituents of the underground parts of Glehnia littoralis. Chem Pharm Bull. 2002; 50(1): 73−77.
29. Wang HL, Wang CM, Li H, Cui XY. Positions and mechanisms of analgesic effect of the from *Radix Angelicae dahuricae.* Chin J Gerontol. 2009; 15: 1902-1904.
30. Nakamura T, Kodama N, Oda M, Tsuchiya S, Arai Y, Kumamoto T, Ishikawa T, Ueno K, Yano S. The structure-activity relationship between oxycoumarin derivatives showing inhibitory effects on iNOS in mouse macrophage RAW26$_{4.7}$ cells. J Nat Med**.** 2009; 63(1): 15-20.

31. Huang G-J, Deng J-S, Liao J-C, Hou W-C, Wang S-Y, Sung P-J, Kuo Y-H. Inducible nitric oxide synthase and cyclooxygenase-2 participate in anti-inflammatory activity of imperatorin from *Glehnia littoralis*. Journal of Agricultural and Food Chemistry. 2012; 60(7): 1673–1681.
32. Liu M, Zhang G, Zheng C, Song M, Liu F, Huang X, Bai S, Huang X, Lin C, Zhu C, Hu Y, Mi S, Liu C. Activating pregnane X receptor by imperatorin attenuates dextran sulphate sodium-induced colitis in mice [Online]. 2018 [cited 2018 Jun 26] Available from: URL: https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bph.14424 https://doi.org/10.1111/bph.14424
33. Wang KS, Lv Y, Wang Z, Ma J, Mi CL, Li XZ, Xu GH, Piao LX, Zheng SZ, Jin XJ. Imperatorin efficiently blocks TNF-α-mediated activation of ROS/PI3K/Akt/NF-$_k$B pathway. Oncol Rep. 2017; 37(6): 3397-3404.
34. Moon TC, Jin M, Son JK, Chang HW. The effects of isoimperatorin isolated from *Agelicae dahuricae* on cyclooxygenase-2 and 5-lipoxygenase in mouse bone marrow-derived mast cells. Arch Pharm Res. 2008; 31(2): 210-215.
35. Shokoohinia Y, Sajjadi S-E, Gholamzadeh S, Fattahi A, Behbahani M. Antiviral and cytotoxic evaluation of coumarins from *Prangos ferulacea*. Pharm Biol. 2014; 52(12): 1543–1549.
36. Rim H-K, Cho W, Sung SH, Lee K-T. Nodakenin Suppresses Lipopolysaccharide-Induced Inflammatory Responses in Macrophage Cells by Inhibiting Tumor Necrosis Factor Receptor-Associated Factor 6 and Nuclear Factor-B Pathways and Protects Mice from Lethal Endotoxin Shock. J Pharmacol Exp Ther. 2012; 342(3): 654–664.
37. Jeong HJ, Na HJ, Kim SJ, Rim HK, Myung NY, Moon PD, Han NR, Seo JU, Kang H, Kim JJ. Anti-inflammatory effect of Columbianetin on activated human mast cells. Bio Pharm Bull. 2009; 32(6): 1027-1031.
38. Lu J, Fang K, Wang , Xiong L, Zhang C, Liu Z, Guan X, Zheng R, Wang G, Zheng J, Wang F. Anti-Inflammatory Effect of Columbianetin on Lipopolysaccharide-Stimulated Human Peripheral Blood Mononuclear Cells. Mediators of inflammation. 2018; 2018.
39. Kang KH, Kong CS, Seo Y, Kim MM, Kim SK. Anti-inflammatory effect of coumarins from *Corydalis heterocarpa* in HT-29 human colon carcinoma cells. Food Chem Toxicol. 2009; 47(8): 2129-2134.
40. Nakamura T, Kodama N, Arai Y, Kumamoto T, Higuchi Y, Chaichantipyuth C, Ishikawa T, Ueno K, Yano S.Inhibitory effect of oxycoumarins isolated from the Thai medicinal

plant *Clausena guillauminii* on the inflammation mediators, iNOS, TNF-α, and COX-2 expression in mouse macrophage RAW 264.7. J Nat Med. 2009; 63 (1): 21–27.

41. Khan S, Shin EM, Choi RJ, Jung YH, Kim J, Tosun A, Kim YS. Suppression of LPS-induced inflammatory and NF-κB responses by anomalin in RAW 264.7 macrophages J Cell Biochem. 2011; 112(8): 2179–2188.
42. Tsai WJ, Chen YC, Wu MH, Lin LC, Chuang KA, Chang SC, Kuo YC. Seselin from *Plumbago zeylanica* inhibits phytohemagglutinin (PHA)-stimulated cell proliferation in human peripheral blood mononuclear cells. J Ethnopharmacol. 2008; 119(1): 67-73.
43. Medina FG, Marrero JG, Macıas-Alonso M, Gonzalez MC, Cordova-Guerrero I, Garciaa AG, Osegueda-Roblesa S. Coumarin heterocyclic derivatives: chemical synthesis and biological activity. Nat Prod Rep**.** 2015; 32(10): 1472-1507.
44. Grover J, Jachak SM. Coumarins as privileged scaffold for anti-inflammatory drug development. RSC Adv. 2015; 5 (49)**:** 38892-38905.
45. Saha A, Payra S, Verma SK, Mandal M, Thareja S, Banerjee S. *In silico* binding affinity to cyclooxygenase-II and green synthesis of benzylpyrazolyl coumarin derivatives. RSC Adv. 2015; 5 (122): 100978–100983.
46. Sethi P, Bansal Y, Bansal G. Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents. Med Chem Res. 2018; 27(1): 61-71.
47. Chavan RR, Hosamani KM. Microwave-assisted synthesis, computational studies and antibacterial/ anti-inflammatory activities of compounds based on coumarin-pyrazole hybrid. R Soc Open Sci. 2018; 5(5): 172435-51.
48. Koparde S, Hosamani KM, Kulkarni V, Joshi SD. Synthesis of coumarin-piperazine derivatives as potent anti-microbial and anti-inflammatory agents, and molecular docking studies. Chemical Data Collections. 2018; doi: 10.1016/j.cdc.2018.06.001
49. Boddu RK, Thummuri D, Naidu VGM, Sistla R, Uppuluri VM. Synthesis of some novel orcinol based coumarin triazole hybrids with capabilities to inhibit RANKL-induced osteoclastogenesis through NF-κB signaling pathway. Bioorg Chem. 2018; 78(8): 94–102.
50. Chougala BM, Samundeeswari S, Holiyachi M, Naik NS, Shastri LA, Dodamani S, Jalalpure S, Dixit SR, Joshi SD, Sunagar VA. Green, unexpected synthesis of bis-coumarin derivatives as potent anti-bacterial and anti-inflammatory agents. Euro J Med Chem. 2017; 143(1): 1744-1756.

51. Holiyachi, M., Samundeeswari, S., Chougala, B.M. et al. Design and synthesis of coumarin–imidazole hybrid and phenyl-imidazoloacrylates as potent antimicrobial and anti-inflammatory agents Monatsh Chem. 2018; 149(3): 595-609.
52. Zhang H-J, Li Y-F, Cao Q, Tian Y-S, Quan Z-S. Pharmacological evaluation of 9,10-dihydrochromeno[8,7-*e*][1,3]oxazin-2(8*H*)-one derivatives as potent anti-inflammatory agent. Pharmacological Reports. 2017; 69(3): 419-425.
53. Dawood DH, Batran RZ, Farghaly TA, Khedr MA, Abdulla MM. New Coumarin Derivatives as Potent Selective COX-2 Inhibitors: Synthesis, Anti-Inflammatory, QSAR, and Molecular Modeling Studies. Arch Pharm. 2015; 348(12): 875–888.
54. El-Haggar R, Al-Wabli RI. Anti-Inflammatory Screening and Molecular Modeling of Some Novel Coumarin Derivatives. Molecules. 2015; 20(4); 5374–5391.
55. Timonen J, Vuolteenaho K, Leppaenen T, Nieminen R, Moilanen E, Aulaskari P, Jaenis J, 7-(2-Oxoalkoxy)coumarins: Synthesis and Anti-Inflammatory Activity of a Series of Substituted Coumarins. J Heterocycl Chem. 2015; 52(5): 1286–1295.
56. Srivastava P, Vyas VK, Variya B, Patel P, Qureshi G, Ghate M. Synthesis, anti-inflammatory, analgesic, 5-lipoxygenase (5-LOX) inhibition activities, and molecular docking study of 7-substituted coumarin derivatives. Bioorg Chem. 2016; 67(8): 130-138.
57. El-Gamal MI, Lee WS, Shin JS, Oh CH, Lee KT, Choi J, Myoung N, Baek D. Synthesis of New Tricyclic and Tetracyclic Fused Coumarin Sulfonate Derivatives and Their Inhibitory Effects on LPS-Induced Nitric Oxide and PGE(2) Productions in RAW 264.7 Macrophages: Part 2. Archiv Der Pharmazie. 2016; 349(11): 853-863.