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Review Article:

A Narrative Review of Benzo-Fused Coumarins, Shedding Light on Their Medicinal Activities

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Abstract

Background: Coumarins and their derivatives excel in chemical diversity, coupled with a wide variety of biological potentials, and tend to be beneficial to the health of the human body. One of these derivatives that has sparked the attention of medicinal chemistry specialists in recent decades is benzo-fused coumarins, which have demonstrated their potential as antioxidants, antimicrobials, antidiabetics, antithrombotics, and many more. **Objective:** This paper discusses the medicinal importance of benzo-fused coumarins derived from natural or synthetic sources. **Conclusion:** The researchers documented that benzo-fused coumarin's basic structure is a promising framework that opens up the chance of discovering innovative applicants with advanced therapeutic potentials.

1. Introduction

Coumarou is the French word that indicates coumarin (**Y**), which is an oxygen-containing heterocyclic product that includes a sizable number of naturally occurring or synthetic chemicals with various biological effects (1). Some examples of these effects include cancer curative (2–7), anti-inflammatory (8–10), oxidative harm preventer (11–14), antimicrobial (15–19), anti-diabetogenic (20), and others.

In addition, *coumarou* has a wide range of uses in chemistry, including fluorescent dyes (21), optical brighteners (22), and lasers (21), as well as uses as an additive in pharmaceuticals, food, and perfumes (23). Newly developed synthetic methods have been used to create a large number of compounds with the *coumarou* scaffold as their basis (24).

According to where the benzene ring is located, there are four different types of benzo-fused coumarins, also known as benzocoumarins, which are coumarins that have been fused with a benzene ring and belong to the family of "π-extended coumarin-based compounds". Benzocoumarin derivatives are divided into four groups according to the location of the fused aromatic ring in **Y** (parent coumarin scaffold): benzo[*h*]coumarin **Y1** (7,8-benzocoumarin), benzo[*g*]coumarin **Y2** (6,7-benzocoumarin), benzo[*f*]coumarin **Y3** (5,6-benzocoumarin), and benzo[*c*]coumarin **Y4** (3,4-benzocoumarin), as shown in Figure 1(25).

Numerous benzo-fused coumarins have been extensively developed in recent years, as a result, attempts to investigate novel therapeutic compounds have been motivated by these coumarins' bioactivities (26). The study team was inspired by these findings to write a review of the medicinal potentials of both synthetic and naturally derived benzo-fused coumarins, with a focus on the most notable examples.

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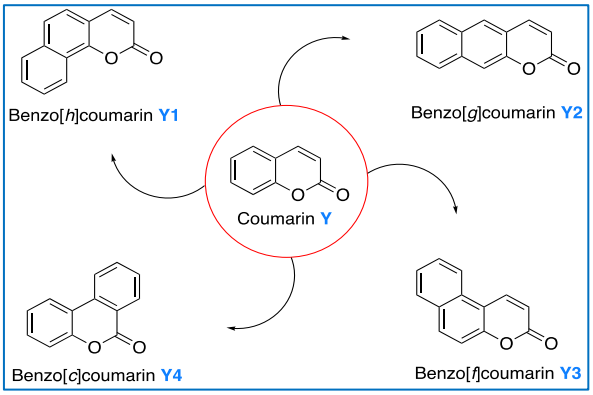

Figure 1: The structural foundations of coumarin and benzo-fused coumarins.

Benzo-fused coumarins' medicinal activities

Benzocoumarins have been of considerable importance because of their diverse range of medicinal potentials, which include antimicrobial (27), antidyslipidemic (28), antioxidant (29), as well as enzyme-inhibitory effects (30) and others (31). So many compounds of benzocoumarin-based structure, whether natural or synthetic, were assessed in chemical laboratories for their bioactivities (26). The following part will review the biological potentials of numerous natural or synthetic benzocoumarin derivatives, along with the upgrade of structurally linked compounds with unprecedented or improved biological activities, and specifically focus on the most significant structural and molecular variables that modify their potentials (26). Figure 2 shows the comprehensive medicinal activities detected for benzocoumarins.

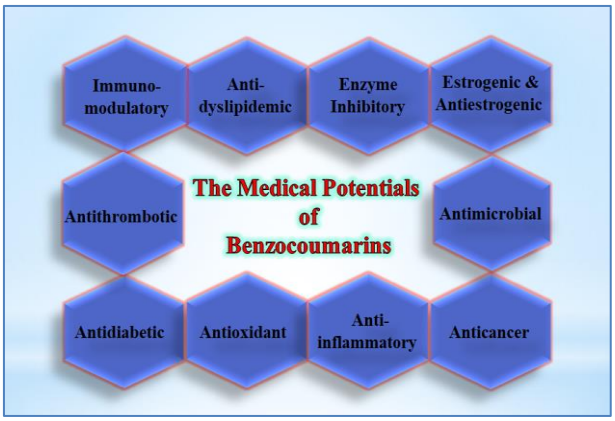

Figure 2: An illustration depicting the medicinal potentials of benzocoumarins.

1.1 Anticancer activity

Zhang and coworkers isolated four benzo[*c*]coumarin derivatives from *Cephalosporium acremonium* IFB-E007 in 2005, which included the new graphislactones G (**Y5**) and H (**Y6**), as well as the previously identified graphislactone A (**Y7**) and alternariol monomethylether (**Y8**), as displayed in Figure 3. The SW1116 cell line's susceptibility to these natural products' anticancer effect was studied. The findings showed that they exhibited a significant anticancer effect against the tested human colon carcinoma cell-line, with IC_{50} levels varying between 8.50 and 21.0 µg/mL (32).

Also, from the *Salvia miltiorrhiza* root, Sun and coworkers isolated a new product of benzo[*h*]coumarin in 2006, known as tanshinlactone A (**Y9**), as demonstrated in Figure 3. The HepG2 (human hepatoma), OVCAR-3 (human ovarian carcinoma), and HeLa (human cervical carcinoma) cell lines were used to test this natural product's anticancer effect. According to the findings, the natural product **Y9** displayed notable cytotoxicity against the investigated cell lines, with IC_{50} levels varying between 6.8 and 8.8 µg/mL (33).

In 2021, Abdul-Ridha and coworkers prepared a new benzo[*f*]coumarin-derived series that was linked with functionalized arylamides or chalcone-esters. The PC-3 cell line (prostatic adenocarcinoma) was used to evaluate these compounds' anticancer effect. From this series, two compounds, herein termed **Y10** and **Y11**, as displayed in Figure 4, exhibited the best cytotoxic activity against the investigated cells, with IC_{50} values of 71.3 µg/mL for **Y10** and 78.2 µg/mL for **Y11** (34).

Recently, Jasim and Mustafa reported the syntheses of a novel series of benzo[*g*]coumarins **(Y12-Y17)**, as shown in Figure 4. The cytotoxicity of this series was assessed against several cell lines, including MCF-7 (breast adenocarcinoma), SKG (cervical carcinoma), SK-OV-3 (ovary adenocarcinoma), AMN3 (mammary adenocarcinoma), Hela (epithelioid cervix carcinoma), and KYSE-30 (esophageal carcinoma). The results revealed that these benzo[*g*]coumarins exhibited cytotoxic activity against the tested cell lines with IC_{50} levels between 13.080 and 100.020 µM, with compound **Y14** being the most promising as an anticancer candidate (35).

1.2 Antioxidant activity

In 2005, from the resident fungal endophyte population cultivated in *Trachelospermum jasminoides*, Song and coworkers isolated graphislactone A (**Y7**), as presented in Figure 3. Against free radicals known as 2,2-diphenyl-1-picrylhydrazyl (DPPH), this natural product demonstrated significant quenching properties, with an IC_{50} level of 2.90 µg/mL. Additionally, it showed greater activity in the removal of hydroxy moieties in a dose-dependent pattern than the reference used. Also, product **Y7** suppressed the generation of reactive species throughout the oxidation of low-density lipoprotein, utilizing cupric ions as an inducer, and showed superior activity than the reference used in the antioxidative test (36).

Sashidhara and coworkers developed new Schiff-base compounds based on a benzo[*h*]coumarin core in 2008 and then assessed the antioxidative properties of these bases. Two of these synthetic benzo[*h*]coumarin-related compounds, **Y18** and **Y19**, as shown in Figure 5, showed the highest inhibition levels among the others against the free moieties used, hydroxyl and superoxide (37).

A new benzo[*f*]coumarins series (**Y20**-**Y30**) was synthesized by Salem and coworkers in 2016, as shown in Figure 5. The ABTS assay was used to assess these compounds' ability to prevent oxidation in homogenized tissues obtained from rats' kidneys and brains. The outcomes of this assessment showed that benzo[*f*]coumarins **Y21**, **Y22**, **Y23**, **Y25**, and **Y27** possessed a significant ability

to prevent oxidation, ranging from 84.40% to 84.60%, while between 69.30 and 75.50%. In addition, the antioxidant activity of **Y24**, **Y28**, and **Y30** was rather moderate and ranged from 43.10% to 56.20% (38).

Y20, **Y26**, and **Y29** had good antioxidant activity ranging

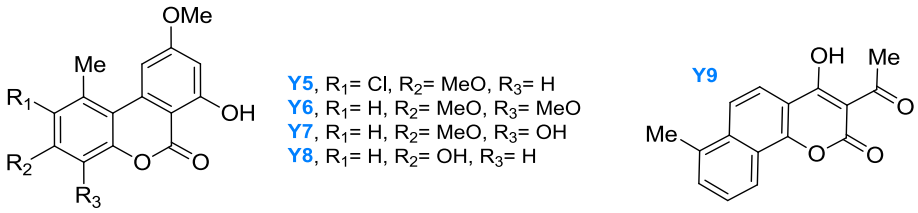

Figure 3: Benzo[*c*]coumarins with cytotoxic potential occur naturally, as demonstrated by Zhang and colleagues (**Y5**-**Y8**) and Sun and colleagues (**Y9**).

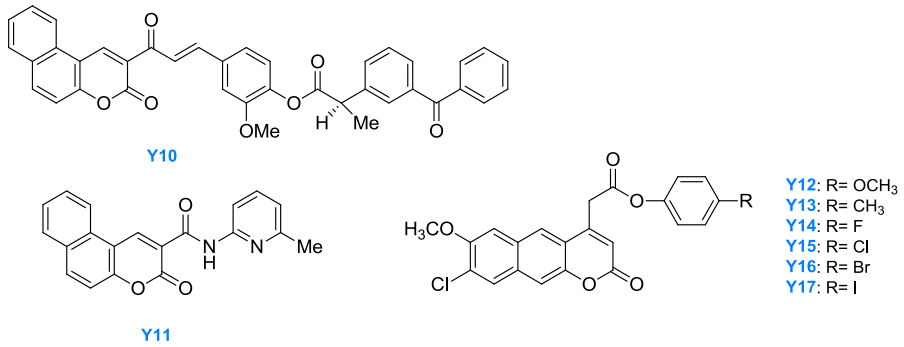

Figure 4: Abdul-Ridha and colleagues (**Y10** and **Y11**) developed benzo[*f*]coumarin-related conjugates with anticancer potential. Also, Jasim and Mustafa's (**Y12**-**Y17**) benzo[*g*]coumarins with cytotoxic potential.

Waheed and Mustafa recently prepared and evaluated the antioxidative potential of a new series of benzo[*g*]coumarin-related compounds (**Y31**-**Y36**), as shown in Figure 5. The authors found that these benzo[*g*]coumarins have a good ability to quench the tested free moieties, with compound **Y33** being the most promising, which had IC_{50} levels of 56.12 µM against DPPH and 59.41 µM against hydroxide free moieties (39).

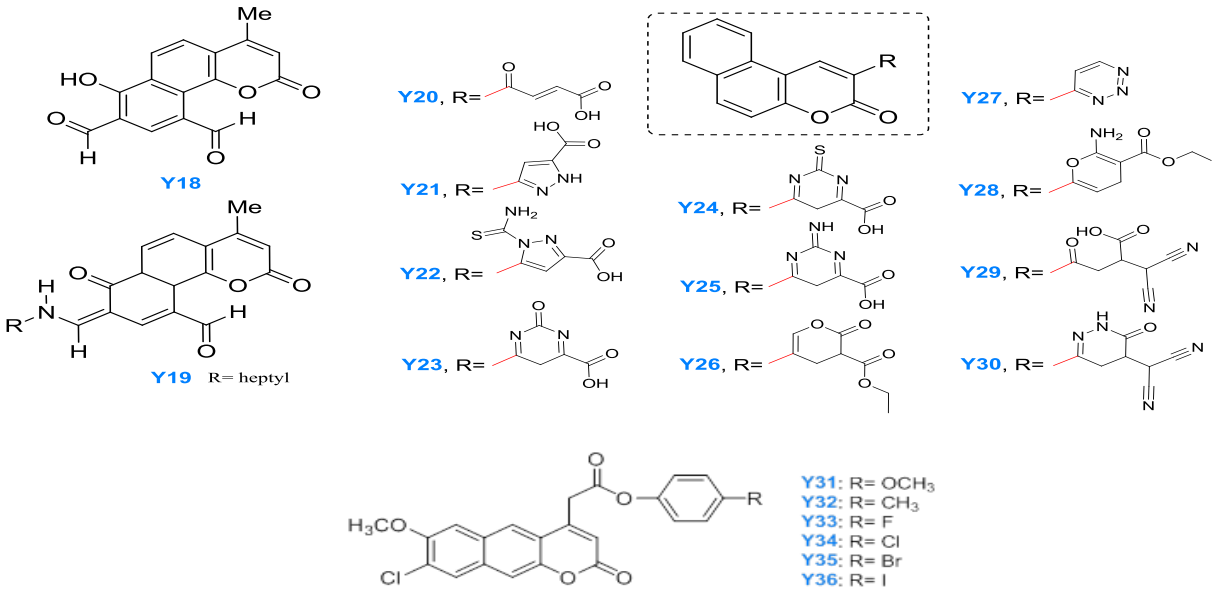

Figure 5: As oxidative inhibitors, Sashidhara and colleagues created benzo[*h*]coumarins (**Y18** and **Y19**). Salem and colleagues synthesized benzo[*f*]coumarins (**Y20**-**Y30**) as free radical quenchers. Furthermore, Waheed and Mustafa's benzo[*g*]coumarin-related compounds (**Y31**-**Y36**) have antioxidant properties.

1.3 Antidiabetic activity

Wiese and coworkers isolated three benzocoumarin derivatives in 2016, namely pannorin (**Y37**), alternariol (**Y38**), and alternariol monomethylether (**Y39**), from *Botryotinia fuckeliana* and *Aspergillus* isolates, and tested their activity on the GSK-3β enzyme. The team found that these derivatives had strong inhibitory activity on the tested enzyme. This good activity may be attributed to the benzocoumarin structure, which has a highly oxygenated core. The chemical structures of these benzocoumarins are illustrated in Figure 6 (40).

Moreover, Mumijo is a famous and distinctive substance that is frequently utilized in traditional medicine systems. It contains a dibenzo-α-pyrone core (**Y4**), as shown in Figure 1, which is responsible for most of its bioactivities. Barouji and coworkers found that it could reduce glucose levels and enhance the activities of superoxide dismutase in the β-cells of the pancreas in diabetic rat models, thus being a promising antidiabetic agent (41).

As mentioned previously, Jasim and Mustafa created a novel series of benzo[*g*]coumarin compounds (**Y12**-**Y17**) in 2022, as depicted in Figure 4, and tested their glucose-lowering capacity against two enzymes, namely, yeast α-glucosidase and porcine α-amylase. The team discovered that **Y12** and **Y13** had the most effective glucose-lowering potential among other prepared benzo[*g*]coumarins (42). Also, in the same year, Waheed and Mustafa synthesized a number of benzo[*g*]coumarins (**Y31**-**Y36**) and evaluated their antidiabetic activity. According to the results, **Y33** and **Y34**, as illustrated above in Figure 5, possessed the strongest suppressive activity on both yeast α-glucosidase and porcine α-amylase enzymes (43).

1.4 Antimicrobial activity

In 2020, Mohamed and coworkers found that urolithin A (**Y40**) and urolithin B (**Y41**), benzo[*c*]coumarin-derived products produced by the gut microbiome, as shown in Figure 7, were able to suppress the Q-S system, which is the communication platform that is crucial for the infectivity of bacteria; therefore, they were effective against carbapenem-resistant *A. baumannii*, *MRSA*, *Campylobacter* species, *S. dysenteriae*, and *V. cholera*. As a result, these urolithins are considered promising candidates for the development of modern antibacterial drugs (44).

In 2022, Megha and coworkers prepared and investigated the antimicrobial activity of new benzo[*g*]coumarin compounds. They discovered that all of the newly synthesized compounds had varying levels of activity against the tested bacterial strains. Four of these benzo[*g*]coumarins (**Y42**-**Y45**), as shown in Figure 7, possessed strong activity against the *B. subtilis* bacterial strain (45).

Also, in 2022, Waheed and Mustafa created a novel set of benzo[*g*]coumarin compounds (**Y31**-**Y36**) and checked their antimicrobial activities. The team discovered that two of the synthesized benzo[*g*]coumarins, **Y33** and **Y34**, as shown in Figure 5, had the most potent activity against all of the bacterial and fungal strains used. This promising activity could be attributed to the chloride and fluoride moieties at position 4″ (46).

Similarly, Jasim and Mustafa prepared another set of benzo[*g*]coumarin compounds (**Y12**-**Y17**) and tested their antimicrobial activities, as presented in Figure 4. As with Waheed and Mustafa, the researchers found that the benzo[*g*]coumarins **Y14** and **Y15**, with chloride and fluoride at position 4″, exhibited the strongest activity against the gram-negative bacteria and fungi strains used. In addition, the intermediate benzo[*g*]coumarin-related compound obtained during the synthesis had promising antifungal activity, while **Y12** possessed good antibacterial activity (47).

1.5 Antithrombotic activity

In 2011, Sashidhara and coworkers reported the synthesis of a novel series of 3-carboxamide-benzo[*h*]coumarins. These compounds were scanned for their antithrombotic effect *in vivo*. The study's results displayed that compound **Y46**, as depicted in Figure 8, exhibited the most potent antithrombotic effect among the tested compounds, even better than the reference. Interestingly, compound **Y46** did not cause an increase in bleeding time. Therefore, it seems to be an attractive candidate for the development of new antithrombotic agents (48).

In 2012, Sashidhara and coworkers prepared and evaluated the antithrombotic effect of a new series of benzo[*h*]coumarin-amides. The authors concluded that some of these prepared compounds (**Y47**-**Y49**), as demonstrated in Figure 8, had a promising antithrombotic effect *in vivo* when compared to the reference (49). Further tests were conducted on compounds **Y47**, **Y48**, and **Y49**, leading to the conclusion that these active molecules significantly reduced collagen- and adenosine diphosphate-induced platelet aggregation. Besides, they resulted in a significant increase in thrombin time. Thus, they possessed antithrombotic activity via both antiplatelet and anticoagulant activity (49).

1.6 Anti-inflammatory activity

In 2015, Lv and coworkers isolated two novel benzo[*h*]coumarins, muralatins A (**Y50**) and B (**Y51**), from *Murraya alata* leaves, as shown in Figure 9. The anti-inflammatory activity of these natural products was screened by measuring their suppressing effect on nitric oxide generation in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. The results revealed that these muralatins exhibited a remarkable suppressing effect on nitric oxide generation as compared to the reference, with IC_{50} values of 12.40 and 9.10 μM, respectively (50).

Recently, Liang and coworkers documented the isolation of two new benzo[*h*]coumarins, murratins C (**Y52**) and D (**Y53**), from *Murraya exotica* twigs and leaves, as illustrated in Figure 9 (51). The activity of these natural products as anti-inflammatory agents was evaluated by estimating their suppressing effect on nitric oxide generation in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. Based on the results, when compared to the reference, the natural product **Y53** possessed a moderate suppressing effect on nitric oxide generation with an IC_{50} value of 39.0 μM, while **Y52** did not show suppression (51).

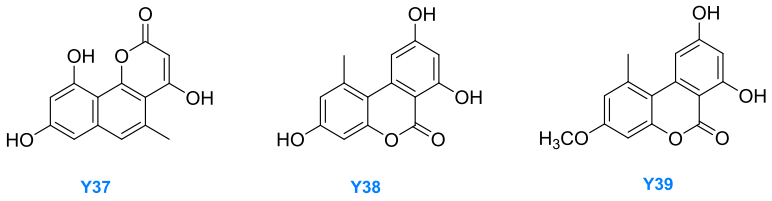

Figure 6: Benzocoumarin derivatives with antidiabetic potential isolated by Wiese and coworkers.

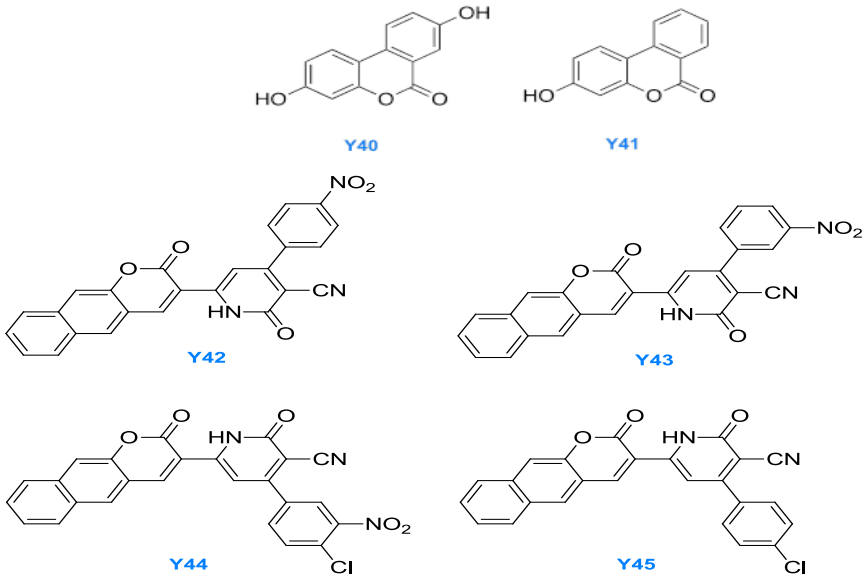

Figure 7: Antimicrobial activity of benzo[*c*]coumarin-related urolithins (**Y40** and **Y41**) reported by Mohamed and colleagues. Megha and colleagues also prepared benzo[*g*]coumarins (**Y42**-**Y45**) with antibacterial potential.

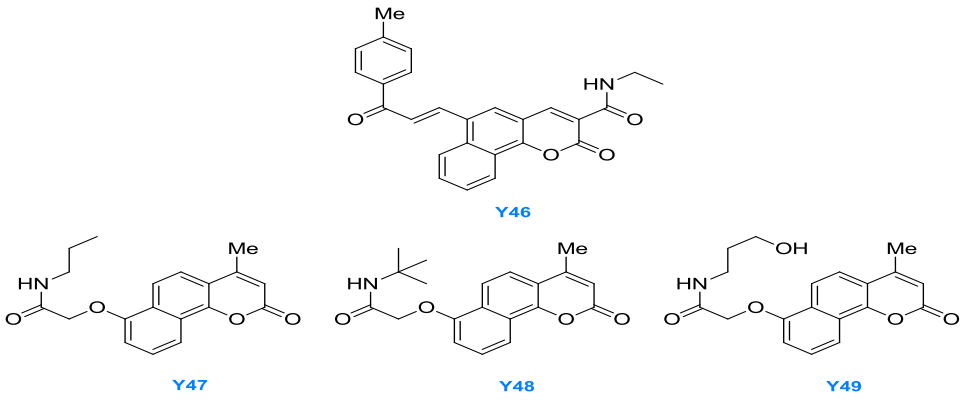

Figure 8: Sashidhara and colleagues synthesized a benzo[*h*]coumarin-derived compound (**Y46**) with antithrombotic activity. Sashidhara and colleagues developed antithrombotic benzo[*h*]coumarins (**Y47**-**Y49**).

1.7 Estrogenic and antiestrogenic activities

In 2006, Larrosa and coworkers studied the estrogenic and anti-estrogenic activity of urolithins A (**Y40**) and B (**Y41**), benzo[*c*]coumarin-derived products produced by the gut microbiome, as displayed in Figure 7. The study results revealed that both urolithins possessed an affinity for α- and β-estrogenic receptors. The binding of **Y40** to the estrogenic receptors was more effective than that of **Y41**. Also, **Y40** affinity for the α-estrogenic receptors was higher than that for the β-estrogenic receptors. In addition, these urolithins demonstrated dose-dependent estrogenic effect (when estradiol is not present) and anti-estrogenic effect (when estradiol is present) (52).

In 2004, Pandey and coworkers prepared a series of substituted benzo[*c*]coumarins and screened their activity as estrogenic receptor agonists and antagonists *in vivo*. According to the study findings, two of the tested compounds, **Y54** and **Y55**, as demonstrated in Figure 10, displayed moderate estrogenic activity with uterine weight gains of 25.0 percent and 21.0 percent greater than the control, respectively (26).

In 2006, Sun and coworkers synthesized a series of functionalized benzo[*c*]coumarins and studied their affinity and selectivity for α- and β-estrogenic receptor subtypes. Based on the findings, the majority of the tested compounds were potent and selective β-estrogenic receptor agonists (53). Compounds **Y56**, **Y57**, **Y58**, and **Y59**, as shown in Figure 10, performed the best, with IC_{50} values ranging between 4.1 and 7.8 nM and selectivity over α-estrogenic receptors ranging from 29 to 124-fold. The authors concluded that, for optimum binding and selectivity, small hydrophobic moieties like ethyl and methyl were required in different locations in the molecule (53).

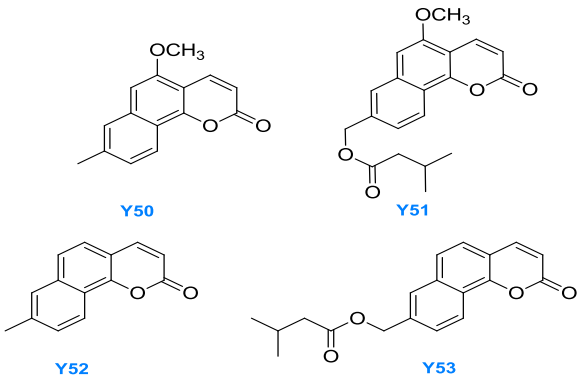

Figure 9: Naturally occurring benzo[*h*]coumarins (**Y50** and **Y51**) with anti-inflammatory potential as reported by Lv and colleagues, as well as those (**Y52** and **Y53**) studied by Liang and colleagues.

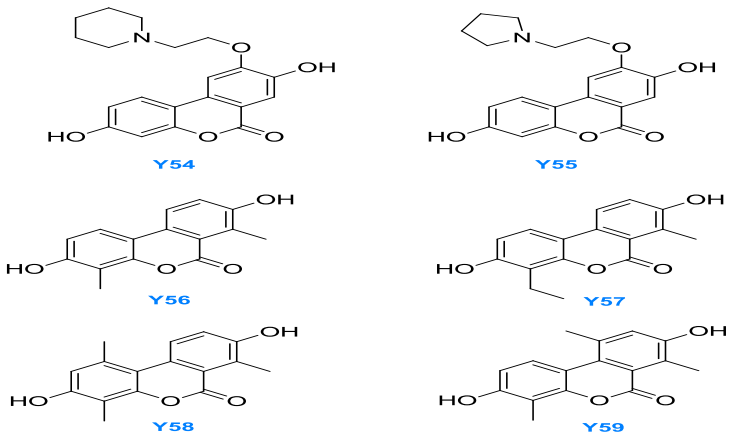

Figure 10: Benzo[*c*]coumarins with estrogenic activity (**Y54** and **Y55**) synthesized by Pandey and colleagues, and those (**Y56**-**Y59**) synthesized by Sun and colleagues.

1.8 Enzyme inhibitory activity

In 1991, Ogawa and coworkers reported the isolation of pannorin (**Y37**), a benzo[*h*]coumarin-derived product, as indicated in Figure 6, from the culture media of the *Chrysosporium pannorum* M10539 fungus. The activity of this natural product was screened towards the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl co-enzyme A reductase. The results revealed that at 160 µM, **Y37** inhibited 50% of the tested enzyme activity (54).

In 2005, Hormazabal and coworkers isolated graphislactone A (**Y7**), an identified benzo[*c*]coumarin-derived product, as illustrated in Figure 3, from the endophytic fungus *Microsphaeropsis olivacea*. The effect of this natural product on the acetylcholinesterase enzyme was assessed. The authors found that **Y7** inhibited acetylcholinesterase moderately, with an IC_{50} value of 8.10 µg/mL (55).

In the same year, 2005, Garino and coworkers prepared four new benzo[*c*]coumarins (**Y60**-**Y63**), as shown in Figure 11. These compounds were subjected to enzymatic inhibitory activity evaluation against nitric oxide synthase, HIV aspartyl protease, serine proteases (trypsin and α-chymotrypsin), and a panel of protein kinases. The results of this evaluation indicated that compounds **Y60**, **Y61**, **Y62**, and **Y63** exhibited modest inhibitory activity on some of the tested enzyme models. Therefore, they are promising starting templates for a drug discovery program (56).

In 2020, Nabeel and coworkers developed a new series of benzo[*f*]coumarins conjugated with anti-inflammatory agents via alkyl-amide linkers (**Y64**–**Y70**), as depicted in Figure 11. The enzymatic inhibitory activity of these compounds was determined *in vitro* against the acetylcholinesterase enzyme. The authors concluded that compounds **Y65**, **Y66**, **Y67**, and **Y69** possessed good inhibitory activity versus the tested enzyme, with IC_{50} values ranging between 1.8 and 8.2 µM, while the other compounds were inactive (57).

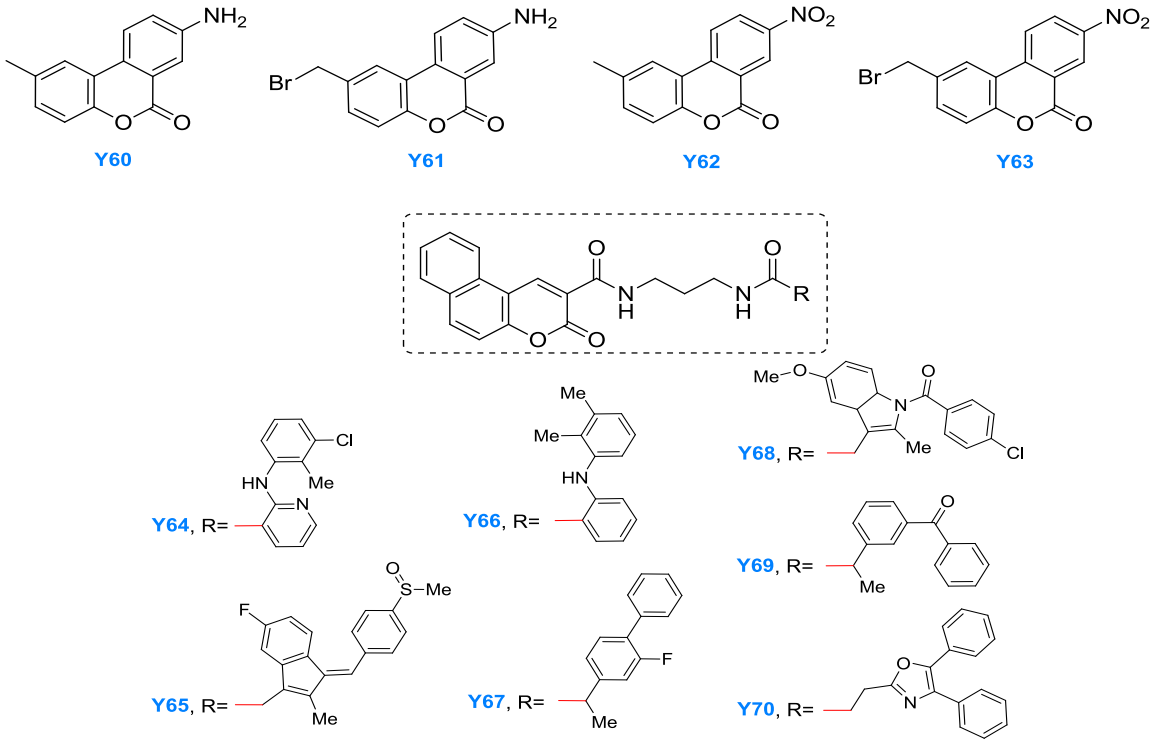

Figure 11: Garino and colleagues created benzo[*c*]coumarins (**Y60**-**Y63**) that inhibit enzymes. Nabeel and colleagues also created benzo[*f*]coumarins (**Y64**-**Y70**) with the same activity type.

1.9 Immunomodulatory activity

In 2007, Wu and coworkers studied the effect of tanshinlactone A (**Y9**), a natural benzo[*h*]coumarin-derived product, on the proliferation of human peripheral blood mononuclear cells (PBMCs) induced by phytohemagglutinin. The outcomes of this study showed that **Y9**, which was identified from *Salvia miltiorrhiza* as shown in Figure 3, had a significant suppressing effect on the proliferation of PBMCs with an IC_{50} value of 15.60 µM. The authors

concluded that **Y9** reduced the production of interferon-γ and interleukin-2 as well as the activation of mitogen-activated protein kinases in PBMCs. Therefore, this natural product was most likely a PBMC immunomodulator (58).

1.10 Antidyslipidemic activity

As stated above, new Schiff-base compounds based on a benzo[*h*]coumarin core have been synthesized by Sashidhara and coworkers. Rats with hyperlipidemia caused by triton were used to test these compounds' antidyslipidemic effectiveness. According to the findings, two of these synthetic benzo[*h*]coumarin-related compounds, **Y18** and **Y19**, as depicted in Figure 5, demonstrated superior ability in lowering levels of tested lipids in plasma. These levels were decreased by 24.0%, 20.0%; 20.0%, 21.0%; and 23.0%, 25.0% for phospholipids, triglycerides, and total cholesterol, respectively (37).

Further, three new series of benzo[*h*]coumarin-related compounds were prepared, and their *in vivo*

antidyslipidemic effect was tested in ongoing investigations by Sashidhara and coworkers. Three of these new benzo[*h*]coumarins (**Y71**-**Y73**), as shown in Figure 12, had a remarkable ability to reduce levels of triglycerides and total cholesterol in plasma. They might therefore be good candidates for the creation of new drugs used in the treatment of hyperlipidemia (59,60).

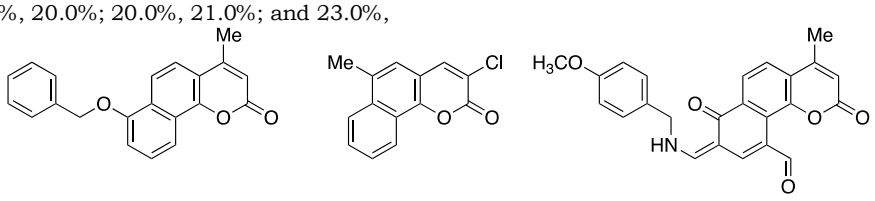

Figure 12: Benzo[*h*]coumarin-related compounds that exhibited antidyslipidemic properties developed by Sashidhara and coworkers.

2. CONCLUSION

The findings of the preceding study afforded three clear-cut conclusions. First, the growing focus on benzo-fused coumarins in pharmaceutical chemistry is due chiefly to their extended pi-conjugated arrangement in comparison to coumarins. Such a feature has sparked the interest of specialists in investigating their bioactive facets. Second, numerous natural and synthetic benzo-fused coumarin derivatives have been proven to have a plethora of therapeutic potentials, including antioxidant, anticancer, antimicrobial, antidiabetic, and many more. Third and finally, the pharmacological potential of the benzo-fused coumarin derivatives succeeds in making them promising therapeutic scaffolds. So, researchers and developers should focus more on creating and developing new benzo-fused coumarins with unique or advanced potentials, in addition to understanding how these derivatives bind to and affect their targets.

3. REFERENCES

1. Jasim SF, Mustafa YF. A review on coumarin backbone: An attractive scaffold for promising bioactive compounds. *Iraqi Journal of Pharmacy*. 2021;18(2):104–125.

2. Mustafa YF, Abdulaziza NT, Jasim MH. 4-Methylumbelliferone and its derived compounds: A brief review of their cytotoxicity. *Egyptian Journal of Chemistry*. 2021;64(4):1807–1816.

3. Mustafa YF, Mohammed NA alwahab. A promising oral 5-fluorouracil prodrug for lung tumor: Synthesis, characterization and releas. *Biochemical and Cellular Archives*. 2021;21:1991–1999.

4. Mustafa YF, Khalil RR, Mohammed ET. Synthesis and antitumor potential of new 7-halocoumarin-4-acetic acid derivatives. *Egyptian Journal of Chemistry*. 2021;64(7):3711–3716.

5. Bashir MK, Mustafa YF, Oglah MK. Synthesis and antitumor activity of new multifunctional coumarins. *Periodico Tche Quimica*. 2020;17(36):871–883.

6. Mustafa YF, Abdulaziz NT. Hymecromone and its products as cytotoxic candidates for brain cancer : A brief review. *NeuroQuantology*. 2021;19(7):175–186.

7. Bashir MK, Mustafa YF, Oglah MK. Antitumor, antioxidant, and antibacterial activities of glycosyl-conjugated compounds: A review. *Systematic Reviews in Pharmacy*. 2020;11(4):175–187.

8. Waheed SA, Mustafa YF. Synthesis of coumarin-based derivatives from different starting materials: A review of ongoing developments. *Iraqi Journal of Pharmacy*. 2022;18(2):126–138.

9. Jebir RM, Mustafa YF. Natural Coumarin-Lead Compounds: A Review of Their Medicinal Potentials. *Iraqi Journal of Pharmacy*. 2022;18(2):139–161.

10. Ismael RN, Mustafa YF, Al-Qazaz HK. Coumarin-based products: Their biodiversity and pharmacology. *Iraqi Journal of Pharmacy*. 2022;18(2):162–179.

11. Khalil RR, Mustafa YF. Phytochemical, antioxidant and antitumor studies of coumarins extracted from Granny Smith apple seeds by different methods. *Systematic Reviews in Pharmacy*. 2020;11(2):57–63.

12. Oglah MK, Kahtan Bashir M, Fakri Mustafa Y, Mohammed ET, Khalil RR. Synthesis and biological activities of 3,5-disubstituted-4-hydroxycinnamic acids linked to a functionalized coumarin. *Systematic Review Pharmacy*. 2020;11(6):717–725.

13. Mustafa YF, Mohammed ET, Khalil RR. Antioxidant and antitumor activities of methanolic extracts obtained

from Red Delicious and Granny Smith apples' seeds. *Systematic Reviews in Pharmacy*. 2020;11(4):570–576.

14. Oglah MK, Mustafa YF. Synthesis, antioxidant, and preliminary antitumor activities of new curcumin analogues. *Journal of Global Pharma Technology*. 2020;12(2):854–862.

15. Mohammed ET, Mustafa YF. Coumarins from Red Delicious apple seeds : Extraction, phytochemical analysis, and evaluation as antimicrobial agents. *Systematic Reviews in Pharmacy*. 2020;11(2):64–70.

16. Mustafa YF, Bashir MK, Oglah MK, Khalil RR, Mohammed ET. Bioactivity of some natural and semisynthetic coumarin derived compounds. *NeuroQuantology*. 2021;19(6):129–138.

17. Mustafa YF, Kasim SM, Al-Dabbagh BM, Al-Shakarchi W. Synthesis, characterization and biological evaluation of new azo-coumarinic derivatives. *Applied Nanoscience* (Switzerland). 2021;(0123456789).

18. Mustafa YF, Khalil RR, Mohammed ET. Antimicrobial activity of aqueous extracts acquired from the seeds of two apples ' cultivars. *Systematic Reviews in Pharmacy*. 2020;11(2):382–387.

19. Mustafa YF, Oglah MK, Bashir MK. Conjugation of sinapic acid analogues with 5- Fluorouracil: Synthesis, preliminary cytotoxicity, and release study. *Systematic Reviews in Pharmacy*. 2020;11(3):482–489.

20. Maoto MM, Beswa D, Jideani AIO. Watermelon as a potential fruit snack. *International Journal of Food Properties*. 2019;22(1):355–370.

21. Gümüş M. Synthesis and characterization of novel hybrid compounds containing coumarin and benzodiazepine rings based on dye. *Journal of Heterocyclic Chemistry*. 2021;58(10):1943–1954.

22. Kumar N, Udayabhanu, Alghamdi AA, Mahadevan KM, Nagaraju G. Solvent free and green synthesis of efficient solvochromism based coumarin moieties for quick visualization of LFPs and OLEDs applications. *Journal of Molecular Structure*. 2021;1223:129208.

23. Russo M, Rigano F, Arigò A, Dugo P, Mondello L. Coumarins, psoralens and polymethoxyflavones in cold-pressed citrus essential oils: A review. *Journal of Essential Oil Research*. 2021;33(3):221–239.

24. Mustafa YF. Classical approaches and their creative advances in the synthesis of coumarins: A brief review. *Journal of Medicinal and Chemical Sciences*. 2021;4(6):612–625.

25. Jung Y, Jung J, Huh Y, Kim D. Benzo[g]coumarin-based fluorescent probes for bioimaging applications. *Journal of Analytical Methods in Chemistry*. 2018;2018:1–11.

26. Lv H ning, Tu P fei, Jiang Y. Benzocoumarins: Isolation, synthesis, and biological activities. *Mini-Reviews in Medicinal Chemistry*. 2014;14(7):603–22.

27. Boutin R, Koh S, Tam W. Recent advances in transition metal-catalyzed reactions of oxabenzonorbornadiene. *Current Organic Synthesis*. 2018;16(4):460–484.

28. Alfei S, Marengo B, Zuccari G. Oxidative stress, antioxidant capabilities, and bioavailability: Ellagic acid or urolithins? *Antioxidants*. 2020;9(8):1–34.

29. Hekal MH, Abu El-Azm FSM, Samir SS. An efficient approach for the synthesis and antimicrobial evaluation of some new benzocoumarins and related compounds. *Synthetic Communications*. 2021;51(14):2175–2186.

30. Channar PA, Irum H, Mahmood A, Shabir G, Zaib S, Saeed A, et al. Design, synthesis and biological evaluation of trinary benzocoumarin-thiazoles-azomethines derivatives as effective and selective inhibitors of alkaline phosphatase. *Bioorganic Chemistry*. 2019;91:103137.

31. Jasim SF, Mustafa YF. A Review of Classical and Advanced Methodologies for Benzocoumarin Synthesis. *Journal of Medicinal and Chemical Sciences*. 2022;5(5):676–694.

32. Zhang H wei, Huang W yang, Song Y chun, Chen J rong, Tan R xiang. Four 6H-dibenzo[b,d]pyran-6-one derivatives produced by the endophyte Cephalosporium acremonium IFB-E007. *Helvetica Chimica Acta*. 2005;88(11):2861–2864.

33. Pratap R, Ram VJ. Natural and synthetic chromenes, fused chromenes, and versatility of dihydrobenzo[h]chromenes in organic synthesis. *Chemical Reviews*. 2014;114(20):10476–10526.

34. Abdul-Ridha NA, Salmaan AD, Sabah R, Saeed B, Al-Masoudi NA. Synthesis, cytotoxicity and in silico study of some novel benzocoumarin-chalcone-bearing aryl ester derivatives and benzocoumarin-derived arylamide analogs. *Zeitschrift für Naturforschung B*. 2021;76(3–4):201–210.

35. Jasim SF, Mustafa YF. New fused-coumarin composites: Synthesis, anticancer and antioxidant potentials evaluation. *Eurasian Chemical Communications*. 2022;4(7):607–619.

36. Song YC, Huang WY, Sun C, Wang FW, Tan RX. Characterization of graphislactone A as the antioxidant and free radical-scavenging substance from the culture of Cephalosporium sp. IFB-E001, an endophytic fungus in Trachelospermum jasminoides. *Biological and Pharmaceutical Bulletin*. 2005;28(3):506–509.

37. Sashidhara K V, Rosaiah JN, Bhatia G, Saxena J. Novel keto-enamine Schiffs bases from 7-hydroxy-4-methyl-2-oxo-2H-benzo[h]chromene-8,10-dicarbaldehyde as potential antidyslipidemic and antioxidant agents. *European Journal of Medicinal Chemistry*. 2008;43(11):2592–2596.

38. Salem MAI, Marzouk MI, El-Kazak AM. Synthesis and characterization of some new coumarins with in vitro antitumor and antioxidant activity and high protective effects against DNA damage. *Molecules*. 2016;21(2):249–269.

39. Waheed SA, Mustafa YF. Synthesis and evaluation of new coumarins as antitumor and antioxidant applicants. *Journal of Medicinal and Chemical Sciences*. 2022;5(5):808–819.

40. Wiese J, Imhoff J, Gulder T, Labes A, Schmaljohann R. Marine fungi as producers of benzocoumarins, a new class of inhibitors of glycogen-synthase-kinase 3β. *Marine Drugs*. 2016;14(11):200.

41. Barouji RS, Saber A, Torbati M, Fazljou SMB, Khosroushahi YA. Health beneficial effects of moomiaii in traditional medicine. *Galen Medical Journal*. 2020;9:e1743.

42. Jasim SF, Mustafa YF. Synthesis and antidiabetic assessment of new coumarin-disubstituted benzene conjugates : An in silico-in virto study. *Journal of Medicinal and Chemical Sciences*. 2022;5(6):887–899.

43. Waheed SA, Mustafa YF. The in vitro effects of new albocarbon-based coumarins on blood glucose-controlling enzymes. *Journal of Medicinal and Chemical Sciences*. 2022;5(6):954–967.

44. Mohamed O, Ammar A, Ilktac M, Gulcan HO. Urolithins and their antimicrobial activity: A short review. *EMUJPharmSci*. 2020;3(2):117–124.

45. Megha G, Bodke YD, Shanavaz H, Joy MN. Substituted benzocoumarin derivatives: synthesis, characterization, biological activities and molecular docking with ADME studies. *Chimica Techno Acta*. 2022;9(4):1–13.

46. Waheed SA, Mustafaa YF. Novel naphthalene-derived coumarin composites: synthesis, antibacterial, and antifungal activity assessments. *Eurasian Chemical Communications*. 2022;4(8):709–724.

47. Jasim SF, Mustafa YF. Synthesis , ADME Study , and antimicrobial evaluation of novel naphthalene-based derivatives. *Journal of Medicinal and Chemical Sciences*. 2022;5(5):793–807.

48. Sashidhara K, Kumar A, Kumar M, Singh S, Jain M, Dikshit M. Synthesis of novel 3-carboxamide-benzocoumarin derivatives as orally active antithrombotic agents. *Bioorganic and Medicinal Chemistry Letters*. 2011;21(23): 7034–7040.

49. Sashidhara K, Palnati GR, Avula SR, Singh S, Jain M, Dikshit M. Synthesis and evaluation of anti-thrombotic activity of benzocoumarin amide derivatives. *Bioorganic and Medicinal Chemistry Letters*. 2012;22(9):3115–3121.

50. Lv HN, Wang S, Zeng KW, Li J, Guo XY, Ferreira D, et al. Anti-inflammatory coumarin and benzocoumarin derivatives from Murraya alata. *Journal of Natural Products*. 2015;78(2):279–285.

51. Liang H, Shi Y, Zeng K, Zhao M, Tu P, Jiang Y. Coumarin derivatives from the leaves and twigs of Murraya exotica L. and their anti-inflammatory activities. *Phytochemistry*. 2020;177:112416.

52. Luca SV, Macovei I, Bujor A, Miron A, Skalicka-Woźniak K, Aprotosoaie AC, et al. Bioactivity of dietary polyphenols: The role of metabolites. *Critical Reviews in Food Science and Nutrition*. 2020;60(4):626–659.

53. Costa M, Dias TA, Brito A, Proença F. Biological importance of structurally diversified chromenes. *European Journal of Medicinal Chemistry*. 2016;123:487–507.

54. Trenin AS. Microbial metabolites inhibiting sterol biosynthesis: Their chemical diversity and characteristics of the mechanism of action. *Russian Journal of Bioorganic Chemistry*. 2013;39(6):565–587.

55. Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. *Biotechnology Advances*. 2020;39:107462.

56. Sasddiqa A, Usman M, Çakmak O. Isocoumarins and 3,4-dihydroisocoumarins, amazing natural products: A review. *Turkish Journal of Chemistry*. 2017;41(2):153–178.

57. Nabeel AAR, Adnan S, Jaber QAH. Development of novel imaging fluorescent agents bearing anti-inflammatory drugs: Synthesis, structural characterization and evaluation of biological activity. *Russian Journal of Bioorganic Chemistry*. 2020;46(4):620–626.

58. Bonito MC, Cicala C, Marcotullio MC, Maione F, Mascolo N. Biological activity of bicyclic and tricyclic diterpenoids from Salvia species of immediate pharmacological and pharmaceutical interest. *Natural Product Communications*. 2011;6(8):1205–1215.

59. Sashidhara K, Kumar M, Modukuri RK, Srivastava A, Puri A. Discovery and synthesis of novel substituted benzocoumarins as orally active lipid modulating agents. *Bioorganic and Medicinal Chemistry Letters*. 2011;21(22):6709–6713.

60. Tejada S, Martorell M, Capo X, Tur J, Pons A, Sureda A. Coumarin and derivates as lipid lowering agents. *Current Topics in Medicinal Chemistry*. 2016;17(4):391–398.