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REVIEW ARTICLE

Dioxolocoumarins: Bridging chemistry and pharmacology with multifunctional therapeutics

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ABSTRACT

Dioxolocoumarin compounds (DCCs) are interesting bioactive molecules that could be used in medicine. They are made up of a coumarin scaffold and a 1,3-dioxolane ring. This review brings together the latest research on both naturally occurring and man-made DCCs, focusing on their wide range of medical benefits and the creative ways they are made to make them work better. DCCs have demonstrated significant activity as anticancer agents, particularly in leukemia and glioma cell lines, owing to their ability to modulate cellular growth pathways and induce apoptosis. In addition, their ability to fight oxidative stress and inflammation makes them a beneficial choice for treating oxidative stress-related diseases. DCCs have strong anticancer properties and have also been shown to be effective against microbial and parasitic pathogens, such as Staphylococcus aureus, Escherichia coli, and Leishmania amazonensis. The part of xanthine oxidase inhibitors shows how DCCs could be used to treat high uric acid and gout. Studies have also demonstrated the anticoagulant, antiviral, and neuroprotective properties of DCCs. This means they can be used to treat a wider range of diseases, including cardiovascular, infectious, and neurodegenerative diseases. Different ways of making DCCs have changed over time, using ring-closing reactions and targeted modifications to make them more biologically active and specific. Structural variations, including substitutions on the coumarin core, have enhanced their pharmacokinetics and potency against specific targets. This review also looks at how DCCs work, which can help us understand the relationships between structure and activity and guide future drug development. DCCs, with their diverse therapeutic potential, present a promising platform for next-generation pharmaceutical development, serving as a bridge between natural product research and innovative drug discovery

Keywords: dioxolocoumarins; pharmacological activity; synthetic methods; anticancer agents; medicinal chemistry

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1. Introduction

A lactone and a benzene ring fuse together to form the large family of ester-containing heterocycles known as coumarins[1–3]. These chemicals are widely distributed in nature and have been isolated through a huge number of investigations from various natural sources, including plants, animals, and microorganisms[4–6]. Also, there is a lot of literature on synthetic methods that use different homogeneous and heterogeneous promoters to make different types of simple and annulated coumarins[7–9]. A lot of research is being done on both naturally occurring[10–12] and man-made[13–15] coumarins to find out what other medical uses they may have besides fighting cancer[16–18], free radicals[19–21], and microbes[22–24]. However, the dioxolocoumarins have attracted poor attention in the literature. This

fact was pointed out by searching the PubMed database for the terms dioxolocoumarins and activity, where only 17 articles were detected, despite the publication date not being restricted. The VOSviewer program matched these articles, yielding **Figure 1**.

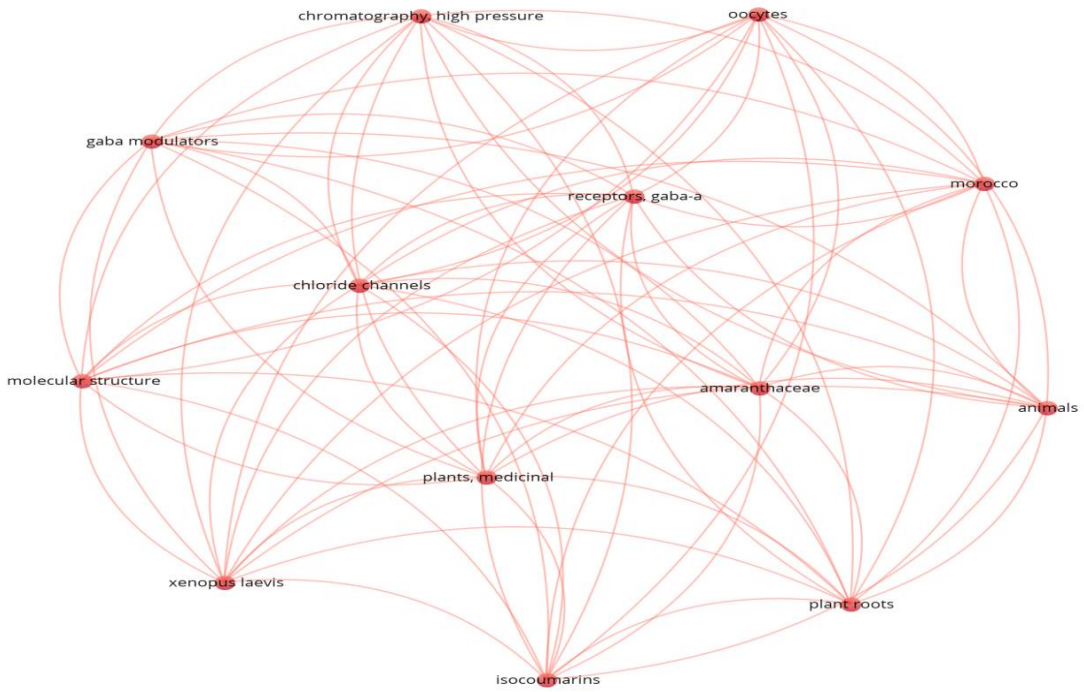


Figure 1. The cross-matching between the dioxolocoumarins and biological activity using the PubMed database.

The 1,3-dioxolane ring has attracted a lot of attention due to its pharmacological properties[25–27]. The result of connecting the dioxolane ring to the coumarin scaffold at points C6 and C7 is shown in **Figure 2**. This made dioxolocoumarin compounds (DCCs), which are known to have many medical uses. Notably, one can chemically create these compounds, which are present in various naturally derived medications[28]. This leading the following sections will address this fused group's medicinal and biological properties.

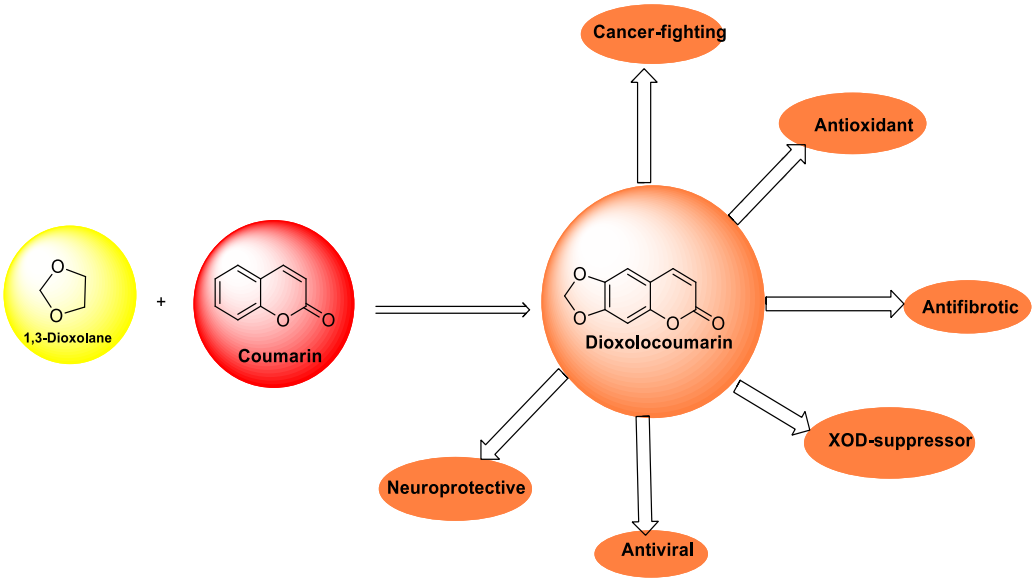


Figure 2. The medicinal functions of natural and synthetic DCCs.

1.1. Natural DCCs, their occurrence and medicinal functions

1.1.1. DCCs as cancer-fighting agents

Riveiro et al., looked into how two DCCs and different extracts from Pterocaulon Polystachyum affected the growth and development of U-937 human promonocytic cells. The only extract type that markedly suppressed cell growth and promoted cell development was petroleum ether[29]. **Figure 3** shows that the DCCs **1** and **2** in the petroleum ether extract slowed down cell growth in a way that depended on the dose and the length of time that they were treated. These DCCs also caused CD88 to work and NBT levels to drop, which are signs of monocytic development. These results suggest that leukemia could benefit from the therapeutic use of DCCs **1** and **2**[30].

Costa et al., identified the DCC **3** molecule from the important oil seed Helianthus annuus. Conversely, other researchers extracted the aerial parts of Pterocaulon virgatum using chloroform[31]. This gave them three regioisomeric structures, which are named here DCCs **4**, **5**, and **6**, as seen in **Figure 3**. After assessing their antioxidant and anti-inflammatory potential, the researchers found that these DCCs have both activities[32].

When Vianna et al., extracted DCCs **1**, **2**, and **7 (Figure 3**) from Pterocaulon species, and these phytochemicals exhibited notable cancer-fighting properties against two types of glioma cells[33]. DCC **1** demonstrated at least two times the potency of DCCs **2** and **7**, with an IC_{50} values of about 34.6 mM against rat glioma cells and 31.6 mM against human U138-MG glioma cells[34]. One possible explanation for this outcome is that DCC **1** adopted a configuration that was planned through a non-classical hydrogen bond between the oxygen of the methylenedioxy groups and the hydrogen of the methoxy[35]. Another significant finding was that the organotypic media did not exhibit the cancer-fighting impact that was produced in glioma cells, suggesting a specific anticancer effect for tumor cells[36].

1.1.2. DCCs as anti-xanthine oxidase agents

Xanthine oxidase is an important enzyme in hyperuricemic syndrome because it helps turn hypoxanthine into xanthine and then into uric acid[37]. Mustafa et al., took DCC **3** from Pterocaulon polystachyum and tested how well it stopped xanthine oxidase in the xanthine/xanthine oxidase system. According to the findings, this phytochemical effectively suppressed the synthesis of uric acid by 60% at a dose of 100 μg/mL [38].

1.1.3. DCCs as anticoagulant agents

Wu et al., took compounds with a DCC scaffold from the airborne part of Artemisia capillaris and named them. These researchers identified these phytochemicals through chemical confirmation and/or spectral analysis. Two of them, DCCs **8** and **9**, as seen in **Figure 3**, had antiplatelet aggregation action [39].

1.1.4. DCCs as antiviral, anti-fibrotic, and neuroprotective agents

From the stems of Kadsura heteroclite, Su et al., extracted DCC **10** (**Figure 3**), which possessed a distinct lignan framework-containing coumarin. Spectroscopic methods, especially 2D NMR and X-ray crystallographic data analysis, were used to figure out the structure of DCC **10** and its exact arrangement [40]. The results of biomedicinal investigations showed that this phytochemical had some anti-fibrotic and neuroprotective effects. It also had great anti-HBV activity against HBeAg and HBsAg [41]. Separately, Stefanachi et al., conducted a focused investigation on DCC **11** (**Figure 3**) that was isolated from a different plant species. Monomethoxy, 3,4,5-trimethoxy, and 4-OH replacement on the 4-phenyl ring were found to make DCC **11** be more helpful than DCC **10**, with an IC_{50} value in the low micromolar level[42].

1.1.5. DCCs as cytochrome 4502A-suppressing agents

Jebir et al., found that plants make phytoalexins, some of which come from the DCC molecular core, to protect themselves from harmful things like fungal infections, chemical damage, and physical damage. Usually, phytoalexins restrict or eliminate invasive elements such as bacteria, viruses, and insects[43]. DCC **3** was initially identified in the Asteraceae-based plant Eupatorium ayapana[44]. Later, this phytochemical was taken from a number of different plants, including Pterocaulon polystachyum, Artemisia apiacea, Helianthus annuus, and Pterocaulon virgatum. In many studies, DCC **3** is regarded as a potent cytochrome P-4502A suppressor[45].

1.1.6. DCCs as antimicrobial agents

Sudan et al., extracted the aerial part of Ageratum fastigiatum looking for the phytochemical DCC **3**, which showed in vitro protection capacity against promastigote forms of Leishmania amazonensis, epimastigote, and L. chagasi. Researchers used HPLC and TLC to analyze the purity and quality of this phytochemical[46–48]. Also, DCC **3** demonstrated interesting antimicrobial activity against many microbes, such as S. aureus, E. coli, P. aeruginosa, and C. albicans. On the other hand, other researchers observed the antimicrobial activity of DCC **3** against T. cruzi, L. chagasi, and L. amazonensis [49]. Additionally, predicted potential targets for this phytochemical as antimicrobial prospect was evaluated by an in silico study [50]. This projected DCC **3** to possess new targets and/or actions, which could guide future research. These findings imply that Ageratum fastigiatum may be a promising source of compounds with antimicrobial and antiparasitic abilities[51].

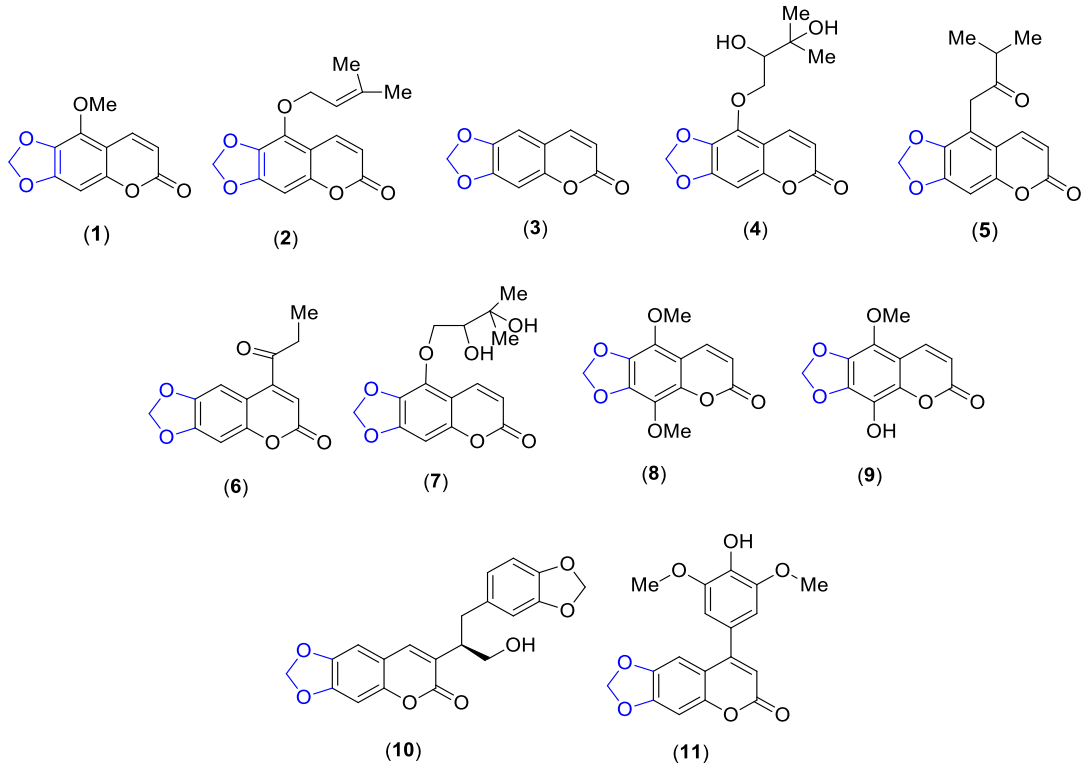


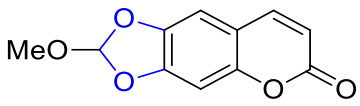
Figure 3. Naturally occurring DCCs having various pharmacological activities.

1.2. Synthetic methods of DCCs and their biomedicinal activities

Litina et al., created linear DCCs 3 and 6. These were better than DMSO at getting rid of hydroxyl radicals, which shows that they are good at quenching hydroxyl radicals. In contrast, other research groups have talked about the ability to scavenge DPPH radicals and stop lipid peroxidation[52]. The results showed

that DCC 6 doesn't have any effect on scavenging DPPH radicals, but it does have some to a lot of effect on stopping lipid peroxidation. Researchers proposed that DCCs 3 and 6 should have a greater anti-inflammatory effect based on these two studies[53].

Son et al., looked into whether the newly made DCCs **3** and **12** (**Figure 4**) could stop rats from getting gastroenteritis when indomethacin was used to cause it in an experimental rat[54]. The researchers created and analyzed these compounds for their gastroprotective properties, and the outcomes revealed that the gastroprotective properties of these two DCCs were equivalent to those of the common medication rebamipide[55]. Additionally, the study indicated that the dioxolane ring caused the gastroprotective effect, while the methoxy group strengthened it[56]. Also, these DCCs didn't have much of an effect on enzymes that break down drugs, and they could lower the short-term side effects of NSAIDs[57].

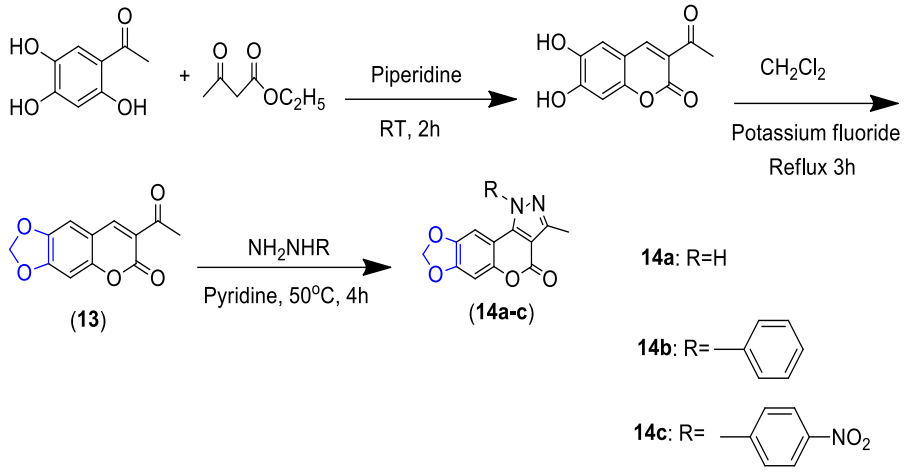


(**12**)

Figure 4. Synthetic DCC with gastroprotective property.

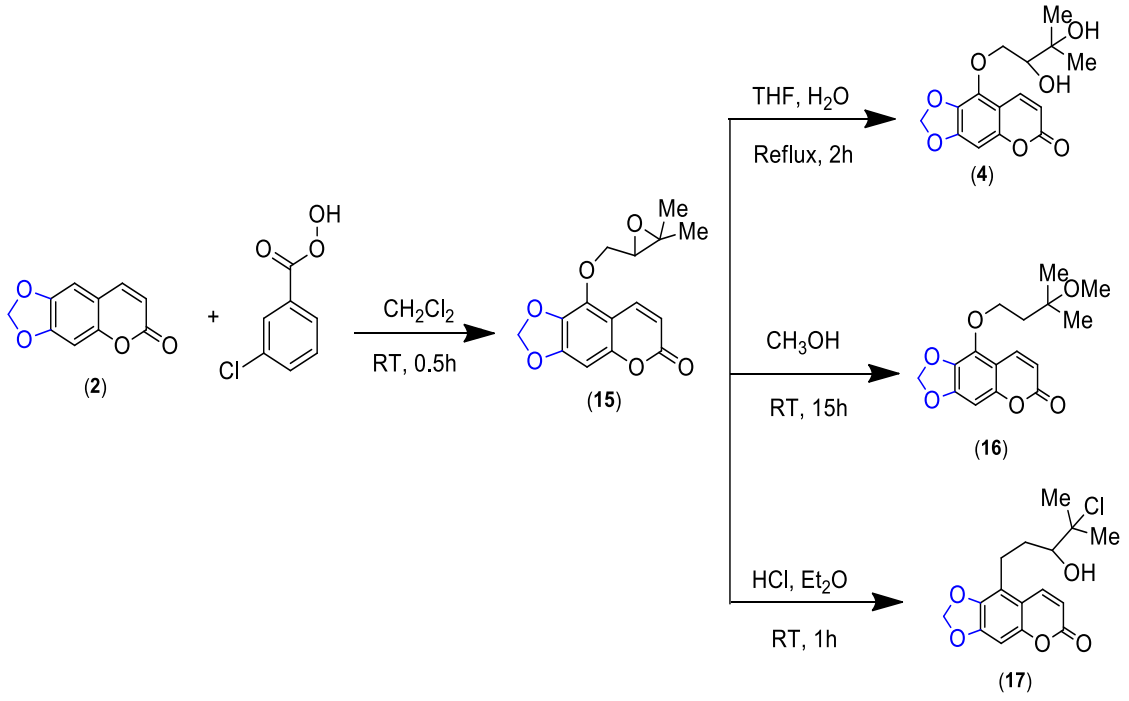
According to Fylaktakidou et al., linear DCCs **3** and **6** were tested to see how well they could react with DPPH. The results showed a weak reaction of 17% and 14%, compared to acetylsalicylic acid (81%). Concerning their ability to compete with DMSO for hydroxyl radical-scavenging, the two DCCs that were tested showed that DCC **3** was the most competitive (41%), while DCC **6** had no effect[58–60]. Also, these compounds were tested to see if they could stop the oxidation of linoleic acid caused by Fe^{2+}. DCC **6** showed the best performance, stopping lipid peroxidation by 44%[61–63].

DCCs **13** and **14** were developed and created linearly by Kahtan et al., using the Konevensgel reaction, generating the former one by condensation of 1-(2,4,5) trihydroxyphenyl)ethenone with ethyl 3-oxobutyrate[64]. After that, it underwent a cyclization reaction using dichloromethane and anhydrous potassium fluoride, resulting in DCC **14**. The last step involved producing intended compounds **14a–c** by reacting hydrazine derivatives with DCC **13**, as shown in **Scheme 1**[65]. Researchers evaluated the ability of the synthesized DCCs to combat cancer by testing them against the malignant lines of the breast cancer (MCF-7) and the esophagus cancer (SKG)[66]. The results demonstrated that DCCs **14a** and **14b** had IC50 values of 8.97 and 11.15 µM against MCF-7, respectively. This was approximately 3.5 times more effective than the standard 5-fluorouracil[67]. The DCCs **14a–c** were more effective at killing cells than the compounds in the dioxole-devoid series, which didn't do anything against SKG and MCF-7. Researchers needed to do more SAR and docking studies to find new compounds that contain dioxole and have strong and specific cancer-fighting effects[68].



Scheme 1. The synthetic pathway followed by Kahtan et al., to create various cancer-fighting DCCs.

Riveiro et al. carried out the creation of several DCCs to assess their anti-leukemic properties. These included a variety of 5-functionalized DCC **3** derivatives, which have been innovatively made readily available through novel creation techniques. Researchers studied these compounds using dbcAMP as a control agent[69]. The naturally isolated DCC **2** served as the starting point for the creation of DCC **4**, **16**, and **17**. The natural product reacted with meta-chloroperoxybenzoic acid to produce the epoxide intermediate DCC **15**[70]. This intermediate went through an epoxide-ring opening reaction, which could have happened in acidic conditions with a mixture of tetrahydrofuran (THF) and water to make DCC **4**, or it could have happened in methanol and HCl to make DCCs **16** and **17**, respectively, where **Scheme 2** illustrates this process[71]. The synthesized DCCs **4**, **15**, **16**, and **17** halted the proliferation of U-937 cells and stimulated their development within 48 hours[72]. Researchers have linked some of the scaffolding properties of polyoxygenated coumarin to their ability to stop leukemia from growing in the lab[73–75].



Scheme 2. The synthetic pathway followed by Riveiro et al, to create various cancer-fighting DCCs.

2. Conclusion

DCCs stand out as a versatile and promising class of molecules with significant pharmacological potential. Their special structure, which is made up of a coumarin core and a 1,3-dioxolane ring, has helped them do many biological properties, like fight cancer and microbes, reduce inflammation, and protect nerve cells. Natural and man-made DCCs have been shown to help with a wide range of illnesses, such as leukemia, gliomas, microbial infections, high uric acid levels, and heart problems. This shows how versatile they are as medicines. The exploration of DCCs has not only advanced our understanding of their medicinal properties but also highlighted the importance of innovative synthetic strategies. These methods have led to structural changes that enhance potency, optimize pharmacokinetics, and effectively target specific disease pathways. Researchers who have looked into how they work, like how they help lower oxidative stress, stop enzymes from working, and change signaling pathways, have learned a lot about how their structure affects their ability to do things. These results make it possible to design next-generation DCC derivatives that work better and are less harmful. Despite these advancements, DCCs still require further research to fully exploit their potential. This includes detailed pharmacokinetic profiling, in vivo studies, and clinical trials to establish safety and efficacy in humans. Moreover, integrating computational tools such as molecular docking and in silico modeling can accelerate drug development process.

3. Future recommendations

Research into DCCs has unveiled their vast therapeutic potential, but there remains significant room for growth in this field. A deeper exploration of the relationship between their structure and biological activity could provide valuable insights. By figuring out which parts of molecules make them work better, researchers can make derivatives that are more specifically and strongly suited for medical uses. Improvements in the methods used to synthesize DCCs could also drive progress. Employing environmentally friendly and cost-effective techniques would not only reduce production expenses but also make these compounds more accessible for large-scale use. Embracing sustainable practices in their synthesis would further align with global efforts to minimize the environmental impact of pharmaceutical production.

While many studies highlight the benefits of DCCs in laboratory settings, rigorous testing in living organisms and clinical trials is essential to confirm their safety and effectiveness in humans. These efforts will help establish the groundwork for introducing DCCs into mainstream medical treatments. Expanding the focus to include underexplored areas, such as rare diseases and metabolic disorders, may reveal new possibilities for their application. Additionally, utilizing computational tools like molecular modeling and virtual screening can fast-track the identification of promising DCC candidates. These technologies offer a more efficient path to discovering compounds with desirable properties. Exploring the potential for DCCs to work in combination with existing treatments could also unlock new therapeutic strategies, particularly for diseases that are difficult to treat.

The effectiveness and safety of DCC-based treatments could be improved with better delivery systems, like nanoparticles or other targeted systems. Such innovations would ensure that these compounds reach their intended targets with minimal side effects. Finally, the continued search for natural sources of DCCs could yield unique analogs and ensure a steady supply of these valuable compounds. By addressing these areas, future research can fully harness the capabilities of DCCs, transforming them into powerful tools in modern medicine.

Conflict of interest

The authors declare no conflict of interest.

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