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REVIEW

Enantio-Enriched Quinic Acid in Anticancer Agents: A Review

SUJARITHA JAYARAJ and HEMALATHA KANAGARAJ*

Department of Pharmaceutical Chemistry, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Thandalam, Chennai-602105, India

*Corresponding author: E-mail: hemalatha6585@gmail.com

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An intriguing avenue for cancer treatment has emerged in the form of enantio-enriched quinic acid, which offers a unique perspective on cancer treatment. In this review, chirality is discussed about drug development and its on the pharmacological properties of quinic acid ($C_7H_{12}O_6$) derivatives. With enantioselective syntheses, quinic acid enantiomers with distinct stereochemistry can be developed, which leads to different biological interactions. This review also emphasizes the anticancer properties of enantio-enriched quinic acid derivatives, identifying particular enantiomers that exhibit increased bioactivity while minimizing off-target effects. Aside from their potency as potent anticancer agents with diminished adverse effects, these compounds often display favourable pharmacokinetic profiles. However, there are still obstacles to overcome, despite the fact that enantioselective synthesis procedures are both scalable and cost-efficient. For these enantiomer-enriched compounds to be validated as safe and effective, extensive *in vivo* investigations and clinical trials are essential. In addition to further research, potential synergistic interactions between these drugs and established therapies should be explored.

Keywords: Quinic acid, Enantiomers, Biosynthesis, Anticancer, Chirality.

INTRODUCTION

The number of people diagnosed with cancer has been steadily climbing over the course of the past few decades, which is a cause for concerned concern. By 2023, there were approximately 1,958,310 cancer patients in the United States, with 609,820 succumbing to this disease [1]. Several types of cancer are particularly common in men, including those affecting the prostate, lungs, colon, rectum and urinary bladder, whereas cancers most commonly occur in women's breasts, rectums, lungs, uterus and thyroids. Consequently, cancer is emerging as a significant global concern that negatively impacts society's quality of life. It is unfortunate that cancer manifests at the tissue level as a diverse array of diseases and that this diversity makes it hard to diagnose cancer accurately, which is further compounded by the ineffectiveness of treatments [2,3]. Men and women both suffer from prostate and breast cancer, which together represent a substantial proportion of all cancer cases. Blood cancer, brain cancer and lymph node cancer, in that order, are the predominant forms of cancer among children [4,5].

There has been an increase in chronic diseases due to significant advancements in technology and therapy. Many of these conditions, which were formerly considered fast lethal a decade or two ago, are now manageable. Treatment progress has had the greatest impact on the oncological conditions. Patients with advanced cancer can benefit from radiation therapy by having less symptoms, either for medicinal or palliative causes. Blood transfusions frequently accompany it and can result in anemia, a decline in leucocyte counts and adjustments in the composition of blood cells [6]. Even more innovative therapeutic interventions to come, individuals battling advanced stage oncology ailments may be able to extend their survival or manage their trajectory more effectively [7]. It seems the most optimal approach to take when considering the increased number of elderly patients is to adopt a comprehensive geriatric assessment [8]. The most effective approach to improving the quality of life for geriatric patients is to utilize a multi-domain care model, transcending traditional approaches to survival and disease management.

In cancer, progressive gene mutations alter cellular functions, signaling the onset of disease. Mutations in genes and

the development of cancerous cells are significantly influenced by chemical compounds. Lung cancer is also significantly exacerbated by smoking due to its exposure to numerous carcinogenic chemicals [9]. Chemical substances that contain carcinogenic properties have both direct and indirect effects on the cytoplasm and nucleus of cells, ultimately resulting in the genetic disturbances [10-13]. About 7% of all cancers are caused by viruses, bacteria and radiation rays. As a general rule, cancer impairs the interplay among cells, resulting in essential genes malfunctioning. Consequently, the disruption causes an aberrant proliferation of the cells [14,15]. In normal conditions, proto-oncogenes control cell division and growth, but when they mutate, they become oncogenes that threaten the viability of cells [16]. According to research, epithelial growth factor receptor mutations cause 30% of breast cancer by disrupting early multi-step carcinogenesis, whereas tumor suppressor gene alterations enhance the risk of epithelial and other malignancies [17]. It is estimated that over 30 different types of repair proteins are encoded by repair genes. UV light exposure triggers primary DNA lesions, which can be prevented by removing uracil from DNA. DNA repair genes play similar roles in these actions. In chronic blood cancer, chromosomal translocation (*e.g.* BCR and Abl genes) contributes to the emergence of oncogenes and genetic abnormalities, as do point mutations (*e.g.* Ras gene), deletions (*e.g.* Erb-B gene), amplifications (such as N-myc in neuroblastoma) and insertions (such as C-myc in acute blood cancer) [18,19].

Chemotherapy and surgery are typically used to treat malignant astrocytomas. Long-term survival remains unfavourable even when advanced treatment approaches are implemented [20]. Squamous cell carcinoma (SCC) in the mouth and lips usually develops from the squamous cells that line the mouth and lips [21]. In most cases, oral cancer occurs without any accompanying pain, arising from growths inside the mouth and tongue. Primary antineoplastic medications are used to treat a variety of solid malignancies, either alone or in conjunction with other chemotherapy regimens and radiation therapy an alternative treatment to surgical excision. Apart from this there are variety of treatment like near-infrared (NIR)-based photoablation therapies, photodynamic therapy, photothermal therapy, *etc*. [22,23].

Quinic acid: According to study outcomes, nutraceuticals which include polyphenols, terpenoids, tannins, alkaloids and flavonoids have the potential to cure fatal diseases such as diabetes, atherosclerosis, cancer, brain disorders and haematological disorders. In a variety of fruits and plants, quinic acid is a naturally occurring organic compound. Apples, berries and coffee beans are all examples of foods that contain it. A cyclic polyol, quinic acid (Fig. 1a) usually IUPAC named as 1a,3R, 4a,5R-tetrahydroxycyclohexane carboxylic acid.The potential of quinic acid as an anticancer agent has been demonstrated across several cancer lines, including oral, cervical and prostate cancers [24-28]. Quinic acid is used to produce pharmaceutically significant chemical compounds, acting as a nutraceutical chiral compound. Plants and microorganisms produce aromatic compounds *via* quinic acid, a biochemical intermediary within the shikimate biosynthetic pathway [29]. Quinic acid can also be synthesized by plants and microbes [30].

A chlorogenic acids, is an ester of (−)-quinic acid derived from hydroxycinnamate. Many plant species synthesize these compounds, with varying quantities and compositions, throughout the plant kingdom. Most notably, caffeic acid, *p*-coumaric and ferulic acids are coupled with quinic acid to form these esters [31]. To investigate the complexities of chlorogenic acid, it is essential to understand that humans ingest around 2-3 g of CGAs daily [32]. The isomeric nature of this chemistry makes it unique. The hydroxyl groups of quinic acid are distinct and all are capable of being acylated to produce monoacyl quinic acid esters, which are regioisomeric. There are six distinct regioisomers when two acyl groups are identical; if the ester substituents differ, there are 12 distinct regioisomers. Moeover, the presence of quinic acid epimers (resulting in six diastereoisomers of quinic acid) and the introduction of *cis-trans* isomerism at the olefinic cinnamoyl moiety augment the complexity. There are 248 isomeric diacyl quinic acids when all these factors are taken into account [33]. The significance of quinic acid is given in Fig. 2.

Natural and synthetic compounds rich in enantiomers: A pivotal concept in chemistry, chirality has been extensively recognized to be important in determining the differences between natural compounds and synthetic pharmaceuticals in terms of their biological activity. The secondary metabolites generated by a wide variety of organisms, such as terrestrial, marine and fungal species, are commonly referred to as natural products. Unlike primary metabolites that are essential for sustaining life, secondary metabolites are capable of sustaining organisms

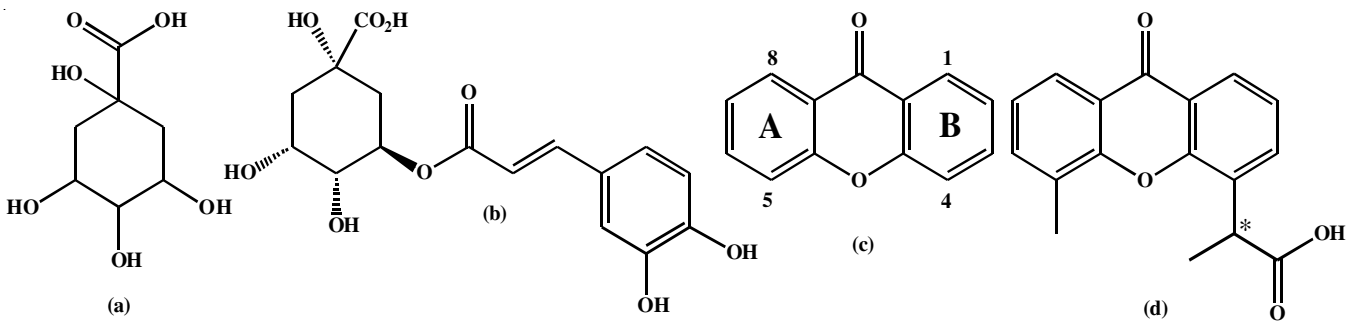

Fig. 1. Structure of (a) quinic acid, (b) chlorogenic acid, (c) xanthone class scaffold compound, (d) chiral analogues of dimethyl xanthone-4-acetic acid

Fig. 2. Therapeutic activity of quinic acid

without their production. However, these often enhance the reproductive strategies and/or defense mechanisms of species producing them [34-37]. Over the last 75 years, biochemists and biologists have devoted considerable attention to uncovering the biosynthesis pathways of bioactive natural products. Nevertheless, the enantiomeric metabolites are generally poorly understood, especially in terms of their biosynthesis. As each organism lives in a chiral milieu and most enzymes exhibit stereoselectivity, it is not surprising that chiral and prochiral compounds, such as pharmaceuticals and agrochemicals, lead to enantiomeric and enantiotopic selectivity in the biological systems. Illustratively, only L-amino acids hold nutritional significance for animals, with L-glutamate serving as a flavour enhancer in food; conversely, the D-isomer lacks such attributes [38].

There are many natural products in the field of medicine that contain a wealth of bioactive agents, including antitumor, antibacterial, anti-insecticidal, anti-helminthic, anti-nematodal, immunosuppressive and other clinically significant effects. Drug discovery and development have largely relied on these attributes. It is very common for chiral natural products to be produced by nature in a state of optical purity, whereby the organism synthesizes only one enantiomer of compound. Various species or genera may produce enantiomeric divergences, resulting in the isolation of a particular enantiomer and its counterpart from another species or genera. An alternative method would be to generate and isolate both enantiomers from a single species using either a racemic mixture or a scalemic mixture, whichever is predominant. As an example, opium poppy plant *Papaver somniferum* synthesizes only the biologically active (–)-isomer of morphine ($C_{17}H_{19}NO_3$) in nature. In contrast, while enantiomeric metabolites are produced and isolated, they are rare in comparison to widespread secondary metabolites [39].

Table-1 listed the details of few plants containing active enantiometric compounds and their therapeutic activity. A variety of organic compounds, such as pyrethroids-pyrethrin I ($C_nH_{28}O_3$) and pyrethrin II ($C_nH_{28}O_5$), feature chiral configurations and specific enantiomers are responsible for their insecticidal efficacy. It is thought that the enantiomeric preference of pyrethroids that have insecticidal properties results from the chiral characteristics of the nerve system that is targeted inside the insect [50]. It has been found that pyrethroids derived from natural products containing multiple chiral centers can be utilized as insecticides with a good level of optical activity. Natural precursors such as chrysanthemic acid and pyrethrolone were commonly used in the syntheses of synthetic pyrethroids in the past, aligning with their specific configurations. Innovative types of synthetic pyrethroids, deviating from natural product precursors while maintaining enantiopurity, have recently been developed [51]. These proce-

TABLE-1
APPLICATIONS OF STEREOISOMERS FROM PLANT SOURCES

S. No	Source	Enantiomeric compounds	Activity	Ref.
1	*Gynoxys szyszylowiczii* Hieron	(*S*)-(+)-α-Phellandrene, (*S*)-(+)-β-phellandrene and (1*S*,2*R*,6*R*,7*R*,8*R*)-(+)-α-copaene	Essential oil	[40]
2	*Ginkgo biloba*	Terpene lactones and flavonol glycosides	Cognitive property	[41]
3	*Illicium oligandrum*	Spirooliganin	Antiviral activity	[42]
4	*Oxaliplatin*	(*R*,*R*)-Cyclohexane-1,2-diamine more active than (*S*,*S*)-cyclohexane-1,2-diamine	Anticancer	[43]
5	*Ricinus communis L.*, seeds	(*R*)-(*Z*)-ricinoleic acid (RA)	Potent antiproliferative and cytotoxic activities	[44]
6	*Peplidiforone* B source: *Hypericum peplidifolium*	*S*-(+)-Skyrin-6-O-β-glucopyranoside (1), *R*-(–)-skyrin-6-O-β-glucopyranoside (2), *S*-(+)-skyrin-6-O-β-xylopyranoside (3), *S*-(+)-skyrin-6-O-α-arabinofuranoside (4)	Mild to moderate depression	[45]
7	*Xanthium sibiricum*	(+)- and (–)-Xanthiazinone A, (+)- and (–)-xanthiazinone B, (+)- and (–)-xanthiazinone C and xanthiazinone D	Anti-inflammatory and cytotoxic activities	[46]
8	Starfish-derived symbiotic fungus *Penicillium sp*	Penicilliode A four pairs of enantiomeric polyketides, penicilliode B and C	Antibacterial, cytotoxic and inhibitory activities against PDE4D2	[47]
9	*Endiandra kingiana*	Three new pentacyclic kingianins	Targeted cancer therapy	[48]
10	Diorganyl dichalcogenides to terminal alkynes using CuI/Zn/glycero	(E)-1,2-*Bis*-chalcogen alkenes	Antioxidant activity	[49]

sses have led to the development of pesticides derived from enantiopure isomers.

The esters containing (1*R*)-(+)-acid moiety show greater insecticidal efficacy than those containing the (1*S*)-(-)-acid moiety [52]. In the synthesizing of synthetic pyrethroids, phenyl-alkanoic acids have emerged as powerful acid moieties. A chiral carbon is often linked to an isopropyl group and these acids have been found to be effective [53]. In a similar manner, herbicidal 2-aryloxypropanoates suppress acetyl-CoA carboxylase enzyme in the body. Enzyme molecules have chiral attributes that contribute to the enantiomeric specificity of these herbicides. The desired biological activity of chiral agrochemicals can be restricted to specific enantiopure isomers, so a number of chiral agrochemicals are manufactured as racemic mixtures, whereas the remaining isomers may be ineffective or even inactive. Both the target organism and the non-target organism may be adversely affected by the undesired stereoisomers. The stereochemistry of agrochemicals and pharmaceuticals has been the subject of countless monographs and reviews in recent years [54-58].

It is found that both chiral isomers of O-methyl O-2,4-dichloro phenyl isopropyl phosphor ramidothioate (DMPA) have potential for regulating plant growth [59]. Condensing saligenin with an optically active thiophosphoryl chloride resulted in optically active bioxabenzofos [60]. O-ethyl O-phenyl phenylphosphonothioate isomers with brucine to develop ^{14}C-labeled compounds for metabolism studies, enantiopure isomers of methamidophos and acephate using similar techniques. It is significant that phosphinothricin, a vital component of bialaphos, was produced *via* asymmetric synthesis with methyl-vinyl-phosphinate and an optically active Schiff base. Some chiral N-substituted azoles show broad-spectrum fungicidal properties, while others regulate plant growth. According to X-ray diffraction, triadimefon possesses a (+)-(8-configuration with one chiral carbon. Although this is true, as the biological activities of its enantiomeric counterparts do not seem significantly different. The resulting triadimenol yields four stereoisomers upon reducing triadimefon. One of the most fungicidal isomers (1*S*,2*R*) emerges [37]. There is a greater potency in (*E*)-isomers than in (*Z*)-isomers, with (*R*)-(-)-isomers having significantly higher fungicidal activity than (*S*)-(+)-isomers. A remarkable difference between the (*S*)-(+)-isomer and the (*R*)-(-)-isomer is that (*S*)-(+)-isomer exhibits greater plant growth regulating abilities. Monochloroanalog uniconazole exhibits this phenomenon even more pronounced. It has been demonstrated that (2*S*,4*R*)-isomer of etaconazole exhibits the highest efficacy against fungi [61-70].

Racemic mixture and its recent development in anticancer agents: As biologically active agents (pharmaceuticals, agrochemicals), additives for altering polymer properties and electronic and optical devices, optically pure chiral molecules have a wide range of applications due to their key role in stereochemistry, an area in chemistry, which has been explored extensively. Since the human body is so remarkably chirally selective, enantiopure medications are crucial for the treatment of illness [66]. Because of this, the approval of enantiopure drugs is on the rise, while approvals for racemic drugs are declining. About 58% of drugs on the market in 2016 were enantiopure, while 8% were racemic compounds, leaving 34% achirals.

Currently, natural sources account for over 60% of anticancer drugs. The development of targeted therapies in the 1990s temporarily displaced this class of bioactive compounds within commercial pharmaceutical research, but interest has recently resurged. From the 1940s to 2010, the FDA studied 175 small molecules for new and approved cancer drugs and discovered that 74.8% came from non-synthetic sources. By combining both enantiomers and utilizing their different interactions in biological systems, racemic mixtures are frequently used in pharmacology to boost therapeutic efficacy. Recent advancements in anticancer drugs, however, have demonstrated the ability to target particular enantiomers in order to maximize therapeutic efficacy and reduce side effects. Through the process of enantiomer isolation and analysis, scientists are gaining insight into the significance of chirality in medication development and laying the groundwork for more individualized and potent cancer therapies. For instance, *R*-enantiomer of the anticancer drug cetuximab was found to be more effective than *S*-enantiomer in stopping the growth of tumors. This understanding has facilitated the development of more precise and effective cancer therapies that center on employing particular enantiomers for [71-75]. Nearly 90% of drugs on the market are racemates or racemic mixtures and over half of today's drugs are chiral compounds. Although chiral drugs are based on the identical chemical structures, their enantiomers can show significant differences in their pharmacology, toxicology, pharmacokinetics, metabolism and other factors. In contrast to one enantiomer that offers therapeutic benefits to the body, the opposite enantiomer poses a considerable risk of toxicity. *R*- and *S*-enantiomers of thalidomide are infamous examples of enantiomer-associated toxicity [76]. The *S*-enantiomers are notorious for causing birth defects at teratogenic levels whereas the *R*-enantiomer exhibits potent sedative properties. 3,4-Dihydroquinazoline compounds are recognized as a prospective anticancer agent [77]. A549 lung cancer cells were shown to be inhibited by KCP-10043F (also known as OZ-001) within this family. Caspases-mediated apoptosis was achieved through STAT3 deactivation, which facilitated caspase-mediated apoptosis.

Research findings indicate that (*R*)-(–)-KCP10043F and (*S*)-(+)-KCP10043F were effectively isolated from the racemate (±)-KCP-10043F (also known as OZ-001) and its anticancer activity was shown using the chiral method of supercritical fluid chromatography [78-80]. A combination of ^{1}H NMR anisotropy and experimental electronic circular dichroism (ECD) was used to determine the absolute configuration of these enantiomers. Taxanes, vinca alkaloids, camptothecins and podophyllotoxins are the primary types of anticancer compounds that are derived from herbal sources (including their partially synthetic derivatives) [81]. Throughout clinical practice, taxanes are vital chemotherapeutic agent. As microtubulin stabilizers, they fall under this category. Pacific yew bark (*Taxus brevifolia*) was originally used to produce paclitaxel, the basic compound in the taxane class [82]. As well as improved pharmacokinetic characteristics, docetaxel is an enhanced anticancer drug [83]. To overcome the limitations associated with paclitaxel and docetaxel, various

structural analogs have been developed [84]. Originally derived from *Catharanthus roseus*, vinca alkaloids disrupt microtubulin function. This group of medications is particularly notable for vinblastine and vincristine, both of which are potent drugs used in the treatment of cancer [85].

A modified lipophilic analog, gimatecan was synthesized as a novel oral camptothecin [86]. Gimatecan inhibits tumor growth in patient-derived xenograft (PDX) models of esophageal squamous cell carcinoma (ESCC). Vinorelbine, vindesine, vincamine and vinflunine are some of the semi-synthetic derivatives developed. The toxicity profiles and effects of these compounds vary significantly [87]. Thus, they find numerous applications in antineoplastic therapy. Even though some compounds are effective against cancer, they are limited in clinical use because of severe adverse reactions, as well as inadequate solubility and bioavailability [88-98]. Numerous semisynthetic derivatives of this compound have been synthesized and evaluated to improve its pharmacological characteristics and mitigate its side effects [99]. In Fig. 3, (a) an asterisk indicates the stereogenic center of melphalan (carbon with four different atoms) and (b) atropoisomeric stereoisomers of gossypol.

It is possible to distinguish stereoisomers based on their stereogenic centers (*R*)-, (*S*)- or their optical activities (+), (–). The interactions between chiral biomolecules and drugs play a crucial role in numerous biochemical processes. Because of this, enzymes and receptors tend to favour one enantiomer over the other. It might be feasible to demonstrate the differences in the biological effects of enantiomers at both a qualitative and quantitative level [100-104].

The enantiomer pairs are binding to a shared binding site differently, thus explaining their distinct activity differences. Enantiomers with more potency must engage in three intermolecular interactions with receptor surfaces, whereas enantiomers with less potency must make only two interactions [105]. In combination with regulatory imperatives and advancements in chemical methodologies, chiral drugs are now being presented for regulatory approval as individual enantiomers rather than racemates as a result of advances in stereoselective synthesis and stereospecific analysis [106]. The anti-inflammatory properties of these drugs have been linked to a reduction in cancer occurrences and recurrences according to numerous scientific studies. As a matter of fact, both *in vitro* and *in vivo* studies have shown that (*R*)-enantiomer of flurbiprofen is effective against colon and prostate cancers [107]. New chemotherapeutic agents are rapidly emerging from exploring the effects of chiral center configurations on biochemical outcomes. The way an anticancer drug interacts with molecular targets in cancer and its structure is affected by its chirality. In addition to organic medicines, metal-based anticancer drugs are also governed by this principle [108]. Several studies have been conducted on chiral metal-based anticancer drugs investigated whether chirality affects the anticancer efficacy of synthetic organic compounds [109]. A literature review examines the antitumor properties of natural and synthetic chiral flavonoids [110-112].

Synthetic quinic acid as a promising therapeutic agent: By using a single enantiomer of quinic acid (+)- and (-)-dragmacidin F variants have been synthesized [113]. These enantiomers have some pivotal commonalities, despite being different synthetic pathways. Reductive isomerization reactions, oxidative carbocyclization reactions, Suzuki couplings specific to certain halogens and Neber rearrangements result in high yields [114]. In the process of synthesis, intricate hurdles are encountered, including the distinct substitutions of pyrazinone, the linked bicyclic ring structure, which fused with both trisubstituted pyrroles and amino imidazoles and the incorporation and retention of 6-bromo indole component [115]. A precise stereochemistry for natural dragmacidin F was not revealed during this synthetic endeavor. In this way, their target compound was chosen arbitrary in terms of its absolute stereochemistry. From an easily accessible (–)-quinic acid, they developed a strategy for generating both versions of dragmacidin F using an enantiodivergent approach. There are multiple pivotal transformations

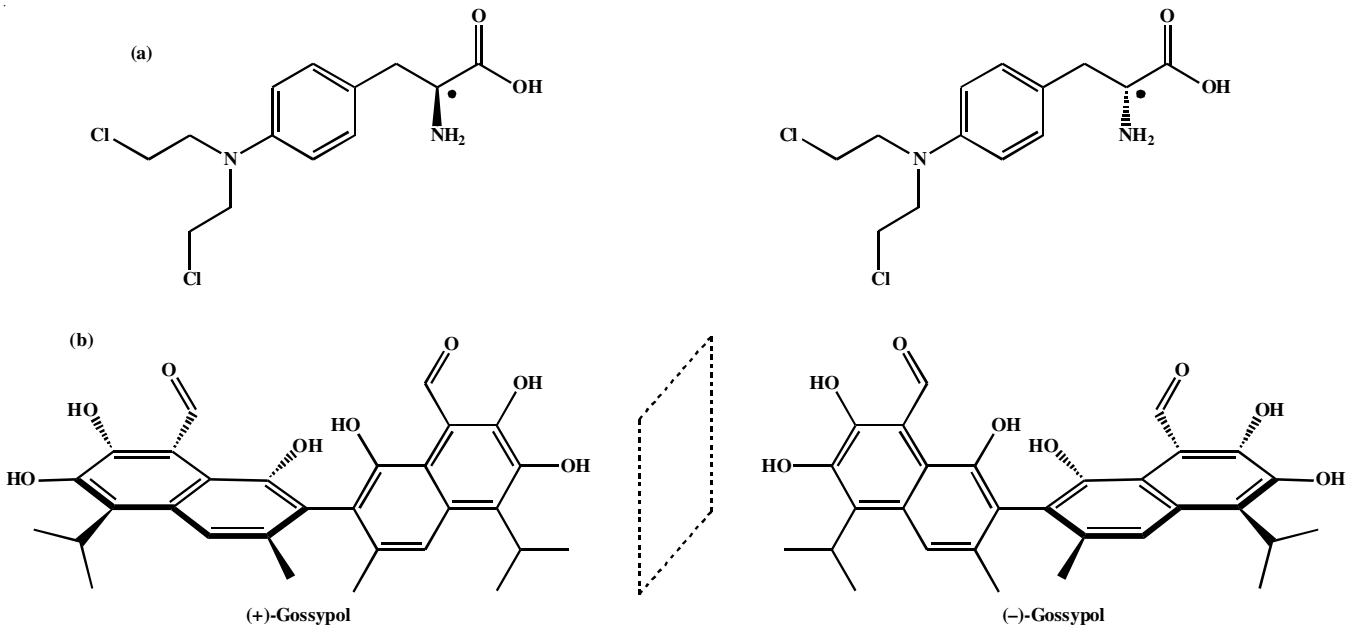

Fig. 3. Enantiomeric pairs in chiral anti-cancer compounds

involved in these routes to (+)- and (−), (a) modifying (−)-16 to differentiate C (3) and C (5); (b) original reductive isomerization reactions; (c) oxidative carbocyclizations mediated by Pd(II) with high steric demands; (d) Suzuki cross-coupling reactions mediated by halogens, and (e) productive Neber rearrangements [116]. In current phase of testing, both variants of dragmacidin F are undergoing extensive biological assessments. The QA-(a)-NPs were also examined as part of an independent investigation of sixteen derivatives of quinic acid (QA) as well as poly(lactic-*co*-glycolic acid) nanoparticles that encapsulated QA-(a) [117,118]. A remarkable 90% inhibition rate was achieved by QA-(a) for cells from LN229 and SNB19, with IC_{50} values of 10.66 M and 28.22 M, respectively. The activation of caspase 3/7 and reactive oxygen species increased along with the initiation of apoptosis, indicating a rapid rate. Accordingly, both QA-(a) and QA-(a)-NPs had comparable cytotoxic effects, suggesting QA-(a) is a potentially effective chemotherapeutic. Synthetically designed enantiomeric compounds are illustrated in Table-2.

Comparison of enantiomeric drugs in anticancer agents: Synthetic quinic acid may have potential benefits in medical fields, the focus on enantiomeric drugs in anticancer agents may offer more immediate and impactful advancements in cancer treatment. Additionally, the complexity of developing and commercializing synthetic quinic acid may present significant challenges that could hinder its widespread use in clinical settings [135].

Chiral xanthones: In addition to possessing chirality, many naturally occurring xanthones have intriguing biological

TABLE-2
VARIOUS ENANTIOMERIC DRUGS AND THEIR THERAPEUTIC ACTIVITY

S. No.	Chiral drugs	IUPAC name	Therapeutic action	Stereoisomers (*R*)	Stereoisomers (*S*)	Ref.
1	Terbutaline	5-[2-(*tert*-Butylamino)-1-hydroxyethyl]benzene-1,3-diol	Bronchodilators	(*R*) is active enantiomer that primarily contributes to the drug's therapeutic effects.	(*S*) is less active or inactive and may contribute to side effects.	[119]
2	Omeprazole	5-Methoxy-2-[[(4-methoxy-3, 5dimethyl-2-pyridinyl)methyl] sulfinyl] benzimidazole	PPI, Peptic ulcer, Zollinger-ellison syndrome	Both enantiomers are converted into the same active form in the acidic environment of the stomach, where they inhibit the H+/K+ ATPase enzyme (the proton pump) in the stomach lining.		[120]
3.	Ketoprofen	2-(3-Benzoylphenyl)-propionic acid	NSAID	(*R*) is less active or inactive in terms of COX inhibition, although it might have other effects or influence the metabolism of the drug.	(*S*) is responsible for the drug's anti-inflammatory and analgesic effects. It inhibits the cyclooxygenase (COX) particularly COX-1 and COX-2, which are involved in the synthesis of prostaglandins (compounds that mediate inflammation, pain and fever).	[121]
4	Citalopram	(1,1-(3-(Dimethylamino) propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile	Anti-depressants	(*R*) is much less active in inhibiting serotonin reuptake and may contribute to some side effects or diminish the overall therapeutic effect.	(*S*) is responsible for the drug's antidepressant effects. It works by selectively inhibiting the reuptake of serotonin (5-HT) in the brain, leading to increased levels of serotonin in the synaptic cleft and enhancing mood	[122]
5	Methylphenidate	Methyl 2-phenyl-2-(piperidin-2-yl)acetate	ADHD & Narcolepsy	(*R*,*R*) for the majority of the drug's therapeutic effects. It has a higher affinity for the dopamine transporter (DAT) and norepinephrine transporter (NET), which leads to increased levels of dopamine and norepinephrine in the brain.	(*S*,*S*) is less active in terms of dopamine and norepinephrine reuptake inhibition and contributes less to the overall therapeutic effect.	[123]
6	Amphetamine	1-Phenylpropan-2-amine	ADHD & Narcolepsy	(*R*) (levoamphetamine) is less potent in terms of stimulant activity but still contributes to the overall effects, particularly in terms of its longer duration of action and effects on norepinephrine release.	(*S*) (dextroamphetamine). It has a higher potency in promoting the release of neurotransmitters like dopamine and norepinephrine, which are responsible for the stimulant effects of amphetamine.	[124]

7	Ofloxacin	7-Fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo trideca-5,6,8,11-tetraene-11-carboxylic acid		Levofloxacin is the name for the pure (*S*)-enantiomer of Ofloxacin. It is more active enantiomer and is commonly used as a more potent and effective antibiotic compared to the racemic mixture of Ofloxacin.	(*S*)-enantiomer is more active against bacterial DNA gyrase and topoisomerase IV, which are the enzymes targeted by fluoroquinolones to inhibit bacterial DNA replication	[125]
8	Naproxen	(2*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid	NSAID	(*R*)-Naproxen is not only inactive in terms of anti-inflammatory effects but can also cause liver toxicity, making it undesirable for use in medications.	(*S*)-Naproxen (dextronaproxen) is responsible for the drug's therapeutic effects. It inhibits the cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which are involved in the synthesis of prostaglandins that mediate pain, inflammation and fever.	[126]
9	Warfarin	4-Hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one	Oral anticoagulant	(*R*)-Warfarin is less active in inhibiting VKOR and contributes less to the anticoagulant effect	(*S*) is the more potent enantiomer, with about 3-5 times. It inhibits the enzyme vitamin K epoxide reductase (VKOR), which is crucial for the synthesis of clotting factors II, VII, IX and X. This inhibition reduces the blood's ability to clot.	[127]
10	Thalidomide	2-(2,6-Dioxopiperidin-3-yl)-hexahydro-isoindole-1,3-dione	Treatment of nausea in pregnant women	(*R*) is associated with the drug's therapeutic effects. It is thought to have anti-inflammatory and immunomodulatory properties, which contribute to its effectiveness in treating multiple myeloma and leprosy-related reactions.	(*S*) is the enantiomer responsible for the drug's teratogenic effects, which can cause severe birth defects when taken during pregnancy.	[128]
11	Ketamine	(*S*)-(+) and (*R*)-(−)- 2-(2-chlorophenyl)-2-(methylamino) cyclohexanone	Anaesthesia	(*R*) While less potent in terms of NMDA receptor antagonism, found to have a longer duration of action. It may also have a different profile of side effects compared to (*S*)-ketamine.	(*S*) This enantiomer is active in terms of its anesthetic and antidepressant effects. It has a higher affinity for the NMDA (N-methyl-D-aspartate) receptor, which is involved in its anesthetic properties. Additionally, (*S*)-ketamine is believed to be more effective in treating depression and is often used in clinical settings for this purpose.	[129]
12	Ibuprofen	2-[4-(2-Methylpropyl)-phenyl]propanoic acid	Anesthetics	(*R*) is less active and has minimal pharmacological effects compared to the (*S*)-enantiomer. It is often considered a prodrug, as it can be converted to the active (*S*)-form in the body through metabolic processes.	(*S*) responsible for the anti-inflammatory, analgesic and antipyretic effects of ibuprofen. It works by inhibiting cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which are involved in the production of prostaglandins that mediate pain and inflammation.	[130]
13	Bupivacaine	(1-ButylN-(2,6-dimethylphenyl) piperidine-2-carboxamide	Local anesthetic	(*R*) it is less potent than the (*S*)-enantiomer, it may still contribute to the overall anesthetic effect and can influence the drug's pharmacokinetics	(*S*) is more potent and has a longer duration of action compared to the (*R*)-enantiomer. It is responsible for local anesthetic effects. It works by blocking sodium channels in nerves, preventing the transmission of pain signals.	[131]

14	Labetalol	2-Hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide	Hypertension	(*R*) contributes to alpha-adrenergic blocking activity, which further helps in reducing blood pressure by blocking α-adrenergic receptors.	(*S*) is responsible for β-adrenergic blocking activity of the drug, which helps to lower blood pressure by blocking β-adrenergic receptors in the heart and blood vessels.	[132]
15	Salbutamol	4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol	COPD	(*R*) It acts as a selective β-2 adrenergic agonist, binding to β-2 adrenergic receptors in the bronchial muscles to cause relaxation and dilation of the airways, improving airflow and alleviating symptoms of asthma and COPD.	(*S*) is less active in terms of β-2 adrenergic receptor binding and contributes less to the drug's therapeutic effects.	[133]
16	Oxaliplatin	*cis*-[(1*R*,2*R*)-1,2-Cyclohexanediamine-*N*,*N*'] [oxalato(2-)-*O*,*O*'] platinum	Metastatic colorectal cancer	*cis* configuration of oxaliplatin contrasts with other platinum-based drugs, such as cisplatin, which has a different ligand arrangement. In cisplatin, the two chloride ions are adjacent, while in oxaliplatin, the oxalate ligand replaces one of the chloride ions		[134]

properties. As chemical molecules, xanthones possess an oxygen containing dibenzopyrone heterocyclic framework, specifically 9*H*-xanthen-9-ones from a structural perspective (Fig. 1c). This category of compounds has proven biological effects, including anticancer and antibacterial activities [136-138].

A primary reservoir of polyprenylated xanthones and benzo-phenones is found in the tropical regions of Asia, Australia and Americas. Several properties of such compounds make them significant antitumor agents. As a result of xanthone action, apoptosis is initiated, cell proliferation is halted, autophagy is induced and telomerase activity is inhibited. They also inhibit angiogenesis, reduce inflammation and counter metastasize [139,140]. Some species of *Garcinia* are cultivated for their fruit or as ornamentals and others are used in indigenous medicine. A trio of enantiomeric polyisoprenylated xanthone pairs, paucinervins L, M and N (Fig. 4) as well as new xanthones, paucinervin O and paucinervin P, have been isolated recently [141]. In addition to discover thirteen new xanthones, these findings were also obtained from the stem of *Garcinia paucinervi*. To evaluate the anticancer potential of the isolated xanthones, three different cell lines: HL-60 myeloid-promyelocytic cells, PC-3 prostate cancer cells and Caco-2 colon adenocarcinomas were investigated. A significant antiproliferative impact was observed among paucinervins L-N against the HL-60 cell line, with IC_{50} values ranging from 0.8 to 8 μM. It wa found that several compounds demonstrated dextrorotation (+), which had more potency than those displaying levorotation (–). In case of paucinervin M, the (–)-enantiomer exhibited cytotoxicity ten-fold greater than that of its (+)-enantiomer [142].

A chiral synthetic derivative of xanthone was assessed for antitumor efficacy. Xanthone-4-acetic acid (Fig. 1d) has been well researched in terms of its pharmacological properties, making synthetic analogs of this compound beneficial [143]. It induces vascular collapse and tumor necrosis through immunomodulation and cytokine activity through the dimethyl derivative of xanthone-4-acetic acid. It was demonstrated that chiral counterparts exhibited enantioselective antitumor effects, causing immediate hemorrhagic necrosis in colon tumors in mice. As observed, the (*S*)-(+) enantiomer of 5-methyl-α-xanthone-4-acetic exhibited significantly greater potency at lower doses than the (*R*)-(–) enantiomer in both *in vitro* and *in vivo* tumor assessments. Rather than merely differing due to the *in vivo* metabolic differences, the enantiomers possess unique inherent activities [144-148].

Baicalin: By using chiral derivatives of baicalin, diverse antineoplastic effects were demonstrated across various cell lines [149]. Traditional Chinese medicine has identified this flavonoid as a promising anti-tumor ingredient derived from *Scutellaria baicalensis* Georg [150]. Baicalin methyl esters were combined with D- or L-phenylalanine methyl esters to synthesize chiral variations. Various chiral baicalin derivatives–BAL (9) (derived from L-phenylalanine methyl ester) and BAD (10) (Fig. 5), were examined *in vitro* and *in vivo* against lung (A549, H460, Calu-1) and breast cancer cells (MBA-M-435, MCF-7, T47D) to determine their antitumor potentials [151]. A549 cell lines, in particular, were found to exhibit heightened inhibition by these synthetic derivatives when compared to pure baicalin. Compared to BAD, BAL displayed significantly higher antiproliferative activity. A549 cells were inhibited by 50 mg/mL of BA, BAD and BAL at 48 h, respectively.

The inhibitory efficacy of BAL and BAD was enhanced in T47D cells relative to baicalin when the two treatments were administered concurrently [152]. In MDA-M-435 cells, BAL and BAD did not inhibit proliferation, but only at high concentrations did they inhibit MCF-7 cells proliferation. Both BAL and BAD were found to be effective at inhibiting subcutaneous tumor growth in mice when used *in vivo*. According to *in vitro* results, BAL was more effective than BAD and baicalin was less effective than baicalin. Apoptosis of tumor cells was enhanced by BAL over BAD and baicalin due to its modulation of phosphatidylinositol 3-kinase signaling [153,154].

Ricinoleic acid: As a naturally occurring fatty acid, (*R*)-(*Z*)-ricinoleic acid (RA) is the main constituent of castor oil derived from *Ricinus communis* seeds. It has been successful in synthesizing numerous RA derivatives with intriguing biological properties [155,156]. These compounds have strong anti-

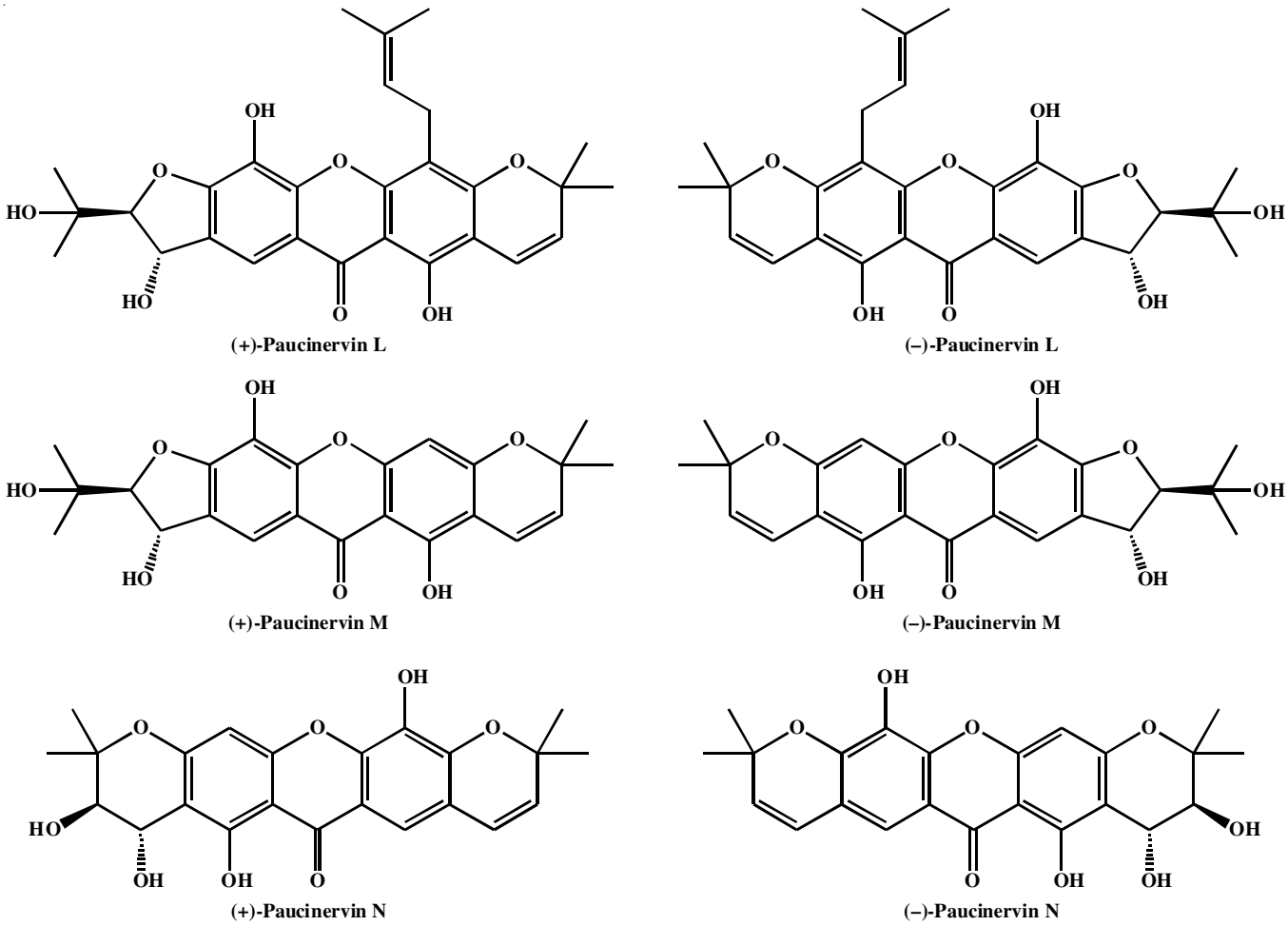

Fig. 4. Chiral paucinervin enantiomers with cytotoxic activity

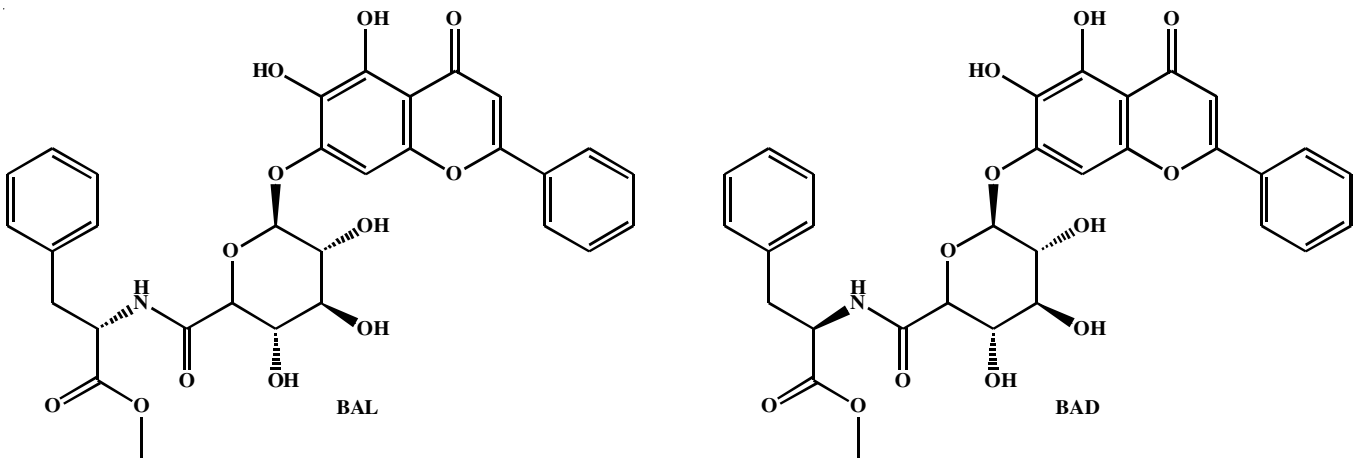

Fig. 5. Structures of chiral baicalin derivatives formed from baicalin and phenylalanine methyl esters-BAL and BAD

proliferative and cytotoxic properties, especially their amides, esters and glycosides. The isolated compounds are found to be more cytotoxic when modified with amines when tested against HT29, HCT116, MCF-7 and AGS cancer cells. In both enantiomeric variants, antitumor effects were observed. Among the most promising cytotoxic results, ethanolamine-derived amides represented the strongest anticancer potential. A researcher synthesized and assessed the cytotoxic effects of ricinoleic acid amides and their corresponding acetates [157]. A study was conducted to investigate the anticancer properties of ricinoleic acid amides and acetate derivatives of ethanolamine amides. The synthesized compounds were tested against HT29, HTC116, AGS and MFC7 cancer cell lines for their cytotoxic properties. DNA damage and necrotic and apoptotic cell death were observed in the compounds under examination. In most instances, only slight variations were observed in the activities of the enantio-

mers. However, there was a significant difference between the (*R*)- and (*S*)-enantiomers in terms of DNA damage induced [158,159].

Anthramycin derivatives: In addition to anthracycline derivatives, actinomycetes synthesize a variety of antibiotics [160-163]. Recently, chiral anthramycin analogs with fused piperazine rings as opposed to pyrrole rings were also synthesized [164,165]. As shown in Fig. 6, various analogs were evaluated for their cytotoxic activity against a variety of cancer cell lines. In cell lines *viz*. MV-4-11 and TCC-UM-IC-3 derived from biphenotypic B myelomonocytic leukemia and human urinary bladder, certain analogs were prepared in enantiomerically pure (S)- and (R)-forms [166]. An IC_{50} value of 0.4 is used as a reference, as is a value of 4.8 for cisplatin. Most of the isolated compounds exhibited comparable cytotoxic effects in both cell lines, with IC_{50} falling within the 10-44 μM range. Among the derivatives containing biphenyl substituents, (S) and (R)-isomers showed a significant difference in enantiomers [167]. It was identified as pivotal structural features that the (S)-configuration and the hydrophobic 4-biphenyl substituent play a role in the cytotoxic effect. Apoptosis and cell cycle arrest at G1/S checkpoints were also linked to the generation of reactive oxygen species in the most effective compounds, according to the study [168-170].

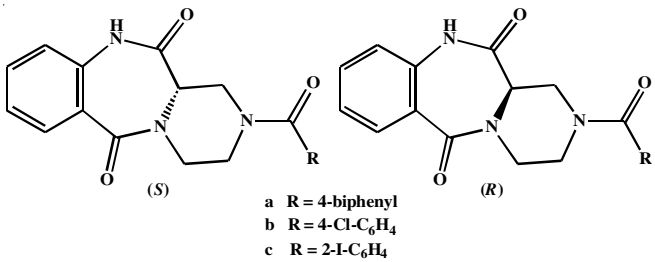

Fig. 6. Structure and cytotoxic activity of the most active enantiomers of anthramycin analogues

Tetrahydroquinolin-8-amines derivatives: A variety of natural alkaloids and synthetic counterparts contain substituted tetrahydroquinolines that have potent biological activity against tumors [171-173]. The ability of aminoquinoline derivatives to induce mitochondrial dysfunction through their ability to elevate reactive oxygen species (ROS) levels is responsible for their antiproliferative potential. Cell lines HeLaS3 and KB-vin, which exhibit multidrug resistance in human cervical cancer, have shown this effect. A series of chiral derivatives derived from 2-methyl-5,6,7,8-tetrahydroquinolin-8-amine has exhibited significant activity against human T-lymphocytes (CEM), cervix carcinomas (HeLa), dermal microvascular endothelial cells (HMEC-1), as well as colorectal adenocarcinoma (HT-29), ovarian carcinoma (A2780) and biphasic mesothelioma (MSTO-211H) cells [174-176].

The biological effects of compounds are often influenced by their spatial arrangement. Similarly, specific cancer cell types responded differently to chiral tetrahydroquinoline derivatives, where enantiomers' cytotoxic effects varied based on their enantiomer. It was observed that the active compounds within the series interact differently with their biological targets by synthesizing them as enantiomerically pure methylphenol derivatives, pyridine derivatives and imidazole derivatives (Fig. 7). *In vitro* antiproliferative activity of both enantiomers of these synthesized compounds was assessed against three human tumor cell lines (HT-29, A2780 and MSTO-211H) [177]. The IC_{50} values of all enantiomers showed significant antiproliferative activity in A2780 cells (ranging from 5.4 to 17.2 μM). The imidazole derivatives showed particularly striking differences in biological activity. A (R)-28 exhibited the greatest efficacy, while a (S)-28 had the least efficacy.

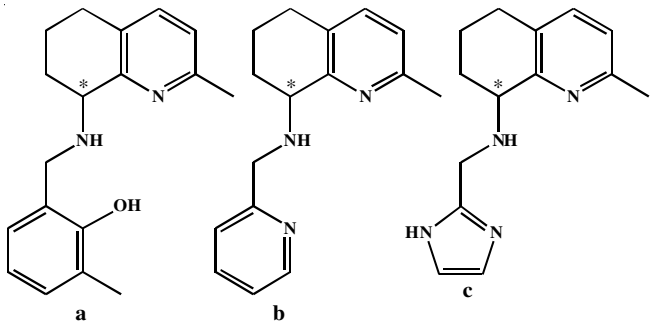

Fig. 7. Structures of the tested tetrahydroquinoline amine derivatives. (*stereo-genic centre)

The IC_{50} values for methyl phenol and pyridine derivatives were comparable despite their chiral variations, indicating a similar cytotoxicity [173]. Similarly, (R)-b and (S)-b both exhibited cytotoxic activity in MSTO-211H cells, whereas neither (S)-a nor (R)-a exhibited activity. Conversely, (S)-cexhibited ineffective growth inhibition, whereas (R)-cexhibited considerable growth inhibition. There was a significant resistance to all synthesized compounds in colorectal adenocarcinoma cells (HT-29), as indicated by IC_{50} values exceeding 20 μM. A study of the mechanism of the cytotoxic effect of (R)-27, the most active pyridine derivative, was conducted. Among A2780 cells, the compound produced cellular reactive oxygen species (ROS) and affected cell cycle phases [178].

Taxol isomers: As a fundamental approach in drug discovery, molecular docking has become increasingly important in probing interactions between ligands and proteins. To identify the most potent chiral paclitaxel isomers, molecular docking investigations of active ligands and proteins were conducted [179]. A number of solid tumor cancers have been shown to be susceptible to paclitaxel, which is commonly known as Taxol®. It has been shown to be effective against breast, ovarian, lung, bladder, prostate, melanoma, esophageal and other solid tumor cancers. Inhibiting mitosis is the mechanism by which the compound exerts its anticancer effects. It is accomplished by increasing tubulin polymerization, which results in microtubule stabilization. *Taxus brevifolia*, yew trees that grow slowly, produce paclitaxel from their bark. There are, however, a number of alternative sources of paclitaxel, since natural sources are limited. As paclitaxel incorporates 11 chiral centers, the chemical structure is complex, making it a difficult target for total synthesis [178-180] (Fig. 8).

A researcher examined the impact of altering the chiral centers of taxol (a) on its binding interaction with β-tubulin,

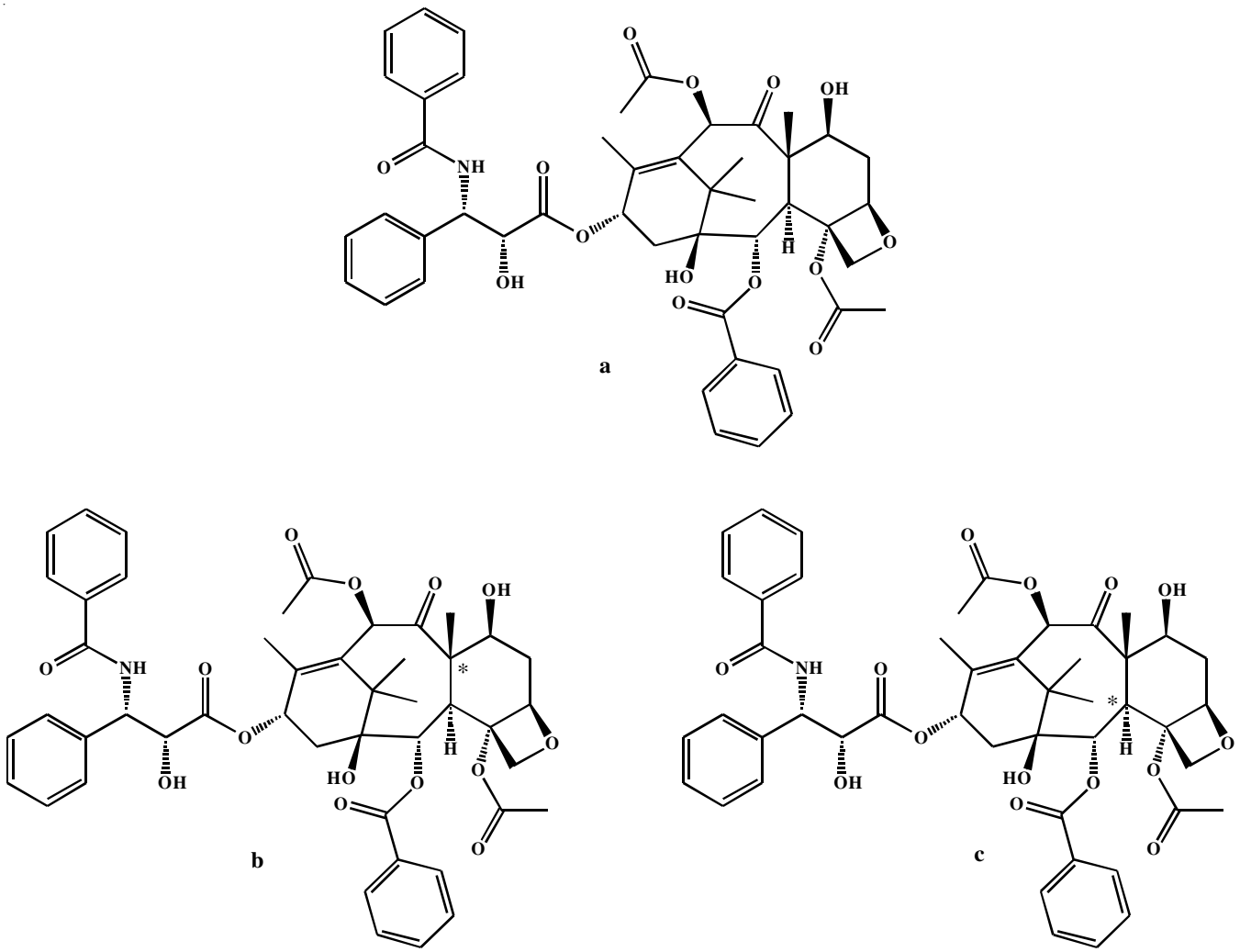

Fig. 8. According to molecular modelling analyses, taxol (a) and its diastereoisomers (b-c) are particularly affine to tubulin. In this case, the asterisk (*) indicates a stereogenic center

employing molecular modelling techniques [181]. Hypothetical ligands were generated by modifying one of the chiral centers at Taxol. Twelve diastereoisomers were evaluated against the binding affinities of the original Taxol structure. A molecular dynamic simulation technique was used to explore the structures with superior binding affinity to the protein based on the docking analysis. The outcomes revealed that structures with reversed configurations at the 5th and 8th chiral centers (b, c) exhibited heightened affinity to β-tubulin compared to Taxol, thus positioning them as promising candidates for further experimental investigations. Comparison with taxol revealed similar affinities for derivatives with reversed 1st, 3rd and 9th chiral centers. This study presents new opportunities for optimizing the production of taxol analogs by removing chiral centers which do not enhance their anticancer efficacy [182-184].

Conclusion

The significance of chirality in medication design and its effect on therapeutic results is highlighted in this review article. Enantio-enriched quinic acid has the potential to be a promising avenue for the development of anticancer agents. Due to enantioselective techniques, quinic acid derivatives may interact with biological targets and pathways differently based on their stereochemistry. There is a significant difference in bioactivity between specific enantiomers and a reduction in off-target interactions for specific enantiomers. Furthermore, such compounds have shown favourable pharmacokinetic profiles that make them potential anticancer agents. While enantioselective synthesis methods are scalable and cost-effective, challenges remain. The safety and efficacy of these enantiomerically compounds must also be validated by comprehensive *in vivo* studies and clinical trials. The mechanistic basis of their anticancer activity remains to be clarified, as does the possibility of synergistic effects when used in combination with existing therapies. As a result, this review illustrates the enormous potential of enantio-enriched quinic acid derivatives in reshaping anticancer drug development. Additional research in this area is expected to pave the way for the development of novel cancer treatments that are both more effective and less potentially harmful.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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