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Coumarin as Anticancer Agents

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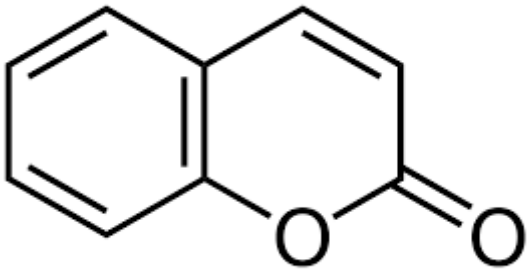
ABSTRACT: Coumarin derivatives are important class of natural plant metabolites that offer variety of biological activities. They can also be derived synthetically, and a wide variety of synthetic coumarin derivatives (azoles, sulfonyl, furan, pyrazole etc) have shown promising anticancer, antitumor and anti-proliferative activities. Coumarin derivatives are not only effective anticancer agents, but also possess minimum side effects. On the basis of different substitution patterns, these potents have displayed tremendous capability to regulate the potential anticancer activities. In view of the above, efforts have been made by the scientists to develop its scaffolds that possess minimal side effects. This review article covers the recent developments of coumarin derivatives that are biologically active against various cancer cell lines. Further, it also highlights the evaluation of these active candidates via in vivo, in vitro, MTT assay. The ongoing developments in the discovery of novel anti-cancer agents and their effectiveness using Structural Activity Relationship is also discussed in detail.

KEYWORDS: coumarin, anticancer, antitumor, assay, agents, synthetic, natural

I. INTRODUCTION

Coumarins are found in higher plants like Rutaceae and Umbelliferae and essential oils of cinnamon bark, cassia leaf, and lavender oil. Coumarin compounds show different biological properties, viz antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-HIV, antihypertension, anticoagulant, anticancer, antiviral, anti-inflammatory, analgesics, antidiabetic, anti-depressive, and other bioactive properties. Coumarin and its derivatives possess anticancer activity against different types of cancers such as prostate, renal, breast, laryngeal, lung, colon, CNS, leukemia, malignant melanoma. In this review, current developments of coumarin-based anticancer agents viz simple coumarin, furanocoumarin, pyranocoumarin, pyrone-substituted coumarin, and their important derivatives have been discussed. The coumarin-triazole, coumarin-chalcone, coumarin-thiosemicarbazone derivatives, and coumarin-metal complexes have been found more potent than coumarin. Hence, further study and structural improvement on coumarin and its derivatives may lead to the design and development of more potent anticancer agents.[1,2,3]



Coumarins are polyphenolic compounds belonging a group of colorless and crystalline oxygenated heterocyclic compounds first isolated from the plant named Dipteryx odorata Willd. (Fabaceae) known locally as “coumaroun” by Vogel in 1820 [1,2]. Oxygenated heterocyclic compounds are furan derivatives with 4C atoms or pyran derivatives with 5C atoms. Although furan derivatives are rarely present in plants, pyran derivatives forming the structure of various compounds are encountered more frequently. The pyran derivatives are ketonic compounds that in the form of α-pyron or γ-pyron. Secondary metabolites called benzo-α-pyrone (coumarin) and benzo-γ-pyrone (chromone) occur due to condensation of pyron derivatives with benzene in plants [3,4].

Coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) and coumarin derivatives are natural compounds that are widely available in plants as a heteroside or free form. A total of 800 coumarin derivative compounds that naturally found were obtained from about 600 genera of 100 families to date [5,6]. Coumarin and its derivatives are frequently found in the seeds, roots and leaves of many plant species belonging to families (especially Rutaceae and Apiaceae) in

the Dicotyledonae class of the division of Spermatophyta. Although most natural coumarins are isolated from vascular plants, some coumarins such as novobiocin, coumermycin and aflatoxin are isolated from microbial sources [7,8].

These compounds have become of importance in recent years due to their various biological activities. Previous biological activity studies performed on coumarin derivatives revealed that these compounds have antitumor [9], photochemotherapy, anti-HIV [10,11], antibacterial and antifungal [12,13], anti-inflammatory [14,15,16], anticoagulant [inhibitors of the enzyme VKOR (vitamin K epoxide reductase)] [17,18], triglycerides lowering [19] and central nervous system stimulant effects [20]. However, a strong antioxidant and protective effect against oxidative stress by scavenging the reactive oxygen species has also been reported for hydroxycoumarins [21]. In addition, the discovery of coumarins with weak estrogenic activity has enabled the usage of this type of coumarins in the prevention of menopausal distress [22]. On the other hand, the usage of some coumarin derivatives as a tobacco flavor, which are used as fixative and flavoring agents, has been regulated by the FDA because of its negative effects, such as mild nausea, diarrhea and hepatotoxicity [23,24,25,26]. Besides their medical use, coumarins are also used in the cosmetic industry and agrochemical industry, as well as optical brightening agents [27,28].

Both natural and synthetic coumarin derivatives draw attention due to their photochemotherapy and therapeutic applications in cancer [29]. It has been reported that substitution patterns can affect the therapeutic, pharmacological and biochemical properties of coumarins in a positive way [18,22,30]. For instance, the substitution of a methoxy group at the 7-position and a 3-methyl 2-butenyl group at the 8-position of the osthol leads to a strong reduction of plasma alkaline transferase (ALT) level in hepatitis and inhibition of caspase-3 activation [31]. Some coumarins have cytostatic effect, while others have cytotoxic activity [32]. It has been revealed to show cytostatic activity of coumarin and its active metabolite, 7-hydroxycoumarin, on human cancer cell lines such as HL-60 (leukemia), MCF-7 (breast), A549 and H727 (lung) and ACHN (kidney). Moreover, cytostatic activity of these compounds against prostate cancer, malignant melanoma and metastatic kidney cell carcinoma has also been reported in clinical studies [32,33,34,35].

Compounds of 3 and 4-hydroxycoumarin structure were determined to inhibit cell proliferation in the gastric carcinoma cell line [36]. In vitro proliferation analysis investigating the mechanism of action of coumarins on the growth and metabolism of MCF-7 and A549 human tumor cells revealed that coumarin was not responsible for observed in vivo effects, but was a precursor of other active metabolites [4]. Previous studies showed that ortho- or meta-dihydroxycoumarins have more cytotoxic effect on human tumor cell lines than mono-hydroxycoumarins [37,38].

In the current review, compilation of various research reports on natural and synthetic coumarin derivatives with anticancer activity and investigation and review of structure–activity relationship studies on coumarin core were aimed. Determination of important structural features around the coumarin core may help researchers to design and develop new analogues with a strong anticancer effect and reduce the potential side effects of existing therapeutics.

Studies conducted on the anticancer activity of coumarin and its derivatives revealed that the mechanism of action of these compounds is generally caspase dependent apoptosis.

CYP 2A6, an isoform of cytochrome P450, metabolizes coumarin to 7-hydroxycoumarin, which has an antiproliferative effect by reducing Bcl expression in various organs and tissues. Bcl-2, a 26 kDa membrane protein, blocks free oxygen radicals, inhibits mitochondrial CYP and suppresses activation of caspase-9, which extends the cell life cycle cumulatively [75]. Thus, it causes carcinogenesis and leads to accumulation of oncogenic mutations in the normal cell. Caspase-9 is activated by Bax, a membrane protein. Over-expression of Bax causes mitochondrial cytochrome C to be released into the cytoplasm through modulation in the mitochondrial membrane. Cytochrome C in the cytoplasm activates caspase-9 and activation of caspase-9 leads to the caspase-3, 6 and 7 activation which breaks down key cytoplasmic and nuclear proteins [76,77].

Coumarins regulate the fate of normal cells by modulating signal transduction pathways containing GTP-binding proteins and reducing Bcl-2 expression. The Bcl-2 protein family consists of Group 1 (Bcl-2 and Bcl-XL), which are apoptotic, and Group 2 (Bax, Bad, Bid and Bak), which are pro-apoptotic. BH1, BH2 and BH3 in the Bcl-2 protein family and their dimerization determine the sensitivity of a cell to negative stimuli [78]. As the ERK/MAPK pathway actively participates in cell proliferation and cytokine production, this pathway is used as an important target for the development of new anticancer agents. This pathway is regulated by MEK1/2 which is activated by direct phosphorylation through MAP3Ks such as ERK1/2, RAFs (a-Raf, b-Raf and c-Raf), COT and MOS [79,80]. Coumarin and its derivatives are one of the highly specific allosteric inhibitors of MEK1/2. MAP3Ks also inhibit the activation of MEK1/2 by inhibiting upstream modulation. However, the activity of activated MEK1/2 is not affected by these compounds [81,82].

Inhibition of the Hsp90 protein is another mechanism in cancer treatment. Novobiocin (Nvb) and other analogs contain coumarin moiety interact with an ATP-linked molecular chaperone that modulates the folding of many proteins, including kinases and transcription factors which are directly related to cancer. Novobiocin and its analogs inhibit the Hsp90 via causing the degradation of Hsp90 proteins by the ubiquitin proteasome pathway.

Cdc25 phosphatases are enzymes that control the eukaryotic cell cycle [83]. Cdk/cyclin are activated by Cdc25A, Cdc25B and Cdc25C enzymes, which are dual specificity phosphatases in normal cell cycle in humans, via the dephosphorylation on pThr14 and/or pTyr15 residues [84]. Cdc25A, Cdc25B and Cdc25C enzymes are involved in the control of the G2/M phase of the cell cycle while the G1/S phase is controlled by Cdc25A [85]. The genomic stability of the living system is maintained by strict regulation of transitions between each of these cell cycle phases. The hyperactivity of Cdc25 phosphatases disrupts this genomic stability, leading to uncontrolled cell growth [84]. These enzymes control and direct each state of cell division. Therefore, they are known as central regulators of the cell cycle [86]. Increased expression of Cdc25A and Cdc25B phosphatases causes negative prognosis in cancer [87]. Many coumarin derivatives, which are potent inhibitors of Cdc25 phosphatase, can be used to control different tumors.

p53 is a transcription factor that stops cell growth and plays an important role in apoptosis. However, apoptosis can also be activated by binding of the target genes to the DNA sequence and activation of p21 and Bax, the promoters of the subgenes. 7,8-Dihydroxy-4-methylcoumarin induces apoptosis by down-regulating p53, Bax, p21 and COX-2, up-regulating c-Myc protein and reducing ERK1/2.

The general structure activity relationship (SAR) and anti-cancer activity of coumarins are presented [4,5,6]

A coumarin compound, esculetin, exhibits many pharmacological effects related with cell proliferation and so antitumor efficacy. Polylactide-co-glycolide (PLGA) nano-micelles formulation of esculetin, nano-esculetin, was prepared to treat against insulinoma INS-1 cells which release more insulin than normal beta cells. Results of this study revealed that administration of nano-esculetin decreased the cell viability more significantly than free esculetin in vitro. Free esculetin also decreased the viability of cells in vitro; however, it has been known that nano-formulations exhibit their superior efficacy at in vivo conditions due to enhanced permeability and retention (EPR) effect. Therefore, nano-formulation of esculetin is thought to be more effective than free esculetin at in vivo conditions [88].

Coumarins in Breast Cancer

The breast tissue is composed of lobules formed by the glands that produce milk, ducts that allow milk to be discharged and fat and connective tissues. Lobes are formed by combination of the lobules, and each breast has 15–20 lobes. The lobules are connected to each other by milk ducts and milk ducts join towards the nipple. The development and physiological functions of the breast are regulated by hormones. The main hormones that provide the development of breast tissue are estrogen and progesterone.

Breast cancer is a systemic disease that occurs when the cells lining the mammary glands and milk ducts proliferate abnormally, spread to various tissues and organs and continue to grow there. It is a complex disease that affects women physically, psychologically and socially [89], and ranks first among cancer types seen in women in the world, and also second most common cause of death due to cancer following the lung cancer [50,90]. In epidemiological studies, the prevalence was found to be 22–26% and the risk of breast cancer-related mortality was around 18% [91,92]. Risk factors related to breast cancer development are summarized in 1.

Since the breast consists of two main structures, there are two types of breast cancer: lobular cancer developing from the milk secreting part and ductal cancer developing from the milk ducts. The most common type of breast cancer is ductal cancer and accounts for 75% of all breast cancers. Breast cancers are histologically divided into two main groups, in situ and invasive carcinomas. In in situ carcinoma, malign epithelial cells are limited in ductus and acinus surrounded by basement membrane while in invasive (infiltrative) carcinoma, neoplastic cells cross the basement membrane and show invasion to the stroma. While the malignant breast tumors have been classified traditionally according to their histological appearance, today some subtypes have been defined according to their molecular features [93,94,95,96]. The subtypes of breast cancers have been identified according to the presence of estrogen receptor (ER) in the light of gene expression studies by Perou et al. for the first time [97]. According to this valid classification, ER positive tumors contain gene expression similar to luminal cells of the mammary glands, cytokeratin profile and markers associated with other luminal cells. In contrast, some of the ER negative tumors are immunohistochemically positive for human epidermal growth factor receptor-2, cerb-B2 (HER2) or HER2 gene amplification may be demonstrated in these tumor cells. This group is known as HER2 positive tumors. HER2 negative luminal non-group tumors show gene expression and immune reactivity similar to normal basal cells of mammary glands. Since ER and progesterone receptor (PR) are also negative in this type of tumors, this group is called basal-like

or triple negative tumor group [97,98,99,100,101]. As a result of studies and meta-analyzes, it was determined that 75% of breast tumors ER and/or PR positive, that is, most tumors are in the luminal group [95]. However, tumors in the luminal group are divided into subtypes as luminal A and B because of their different behaviors. Tumors of luminal A group, which has the highest prevalence among breast cancers, consist of HER2 negative tumors with low proliferative activity, mitotic rate and histological grade. The prognosis of patients with luminal A tumor is good and metastases are often limited to bones. Luminal B tumors are more malignant and the most important difference of this group is that tumors have high proliferation rate. The limit value between luminal A and B is generally considered to be nuclear Ki67 expression immunohistochemically less than 14% of tumor cells.[7,8,9] In addition, approximately 30% of HER2 positive tumors are immunohistochemically in the luminal B phenotype [102,103,104,105,106,107,108,109].

Despite the development of early diagnosis strategies and advances in treatments, breast cancer is still an important reason of mortality and morbidity. Prognostic factors known in breast cancer are lymph node involvement, tumor size, distant metastasis status, tumor cellular differentiation degree, patient's age, state of hormone receptors in tumor, HER2 overexpression, tumor proliferation index, lymphovascular invasion, tumor histology, response to neoadjuvant chemotherapy and hormonotherapy and p53 mutation.

In premenopausal women, high levels of androstenedione compete with aromatase inhibitors in the enzyme complex in cases which estrogen synthesis cannot be completely blocked, and an initial lowering of the estrogen level causes an increase in the level of gonadotropin. The main source of estrogen in postmenopausal women is the conversion of androstenedione released from the adrenal gland into estrogen through the aromatase enzyme in the peripheral tissues [110]. The aromatase inhibitors (AI) used at this stage lower the plasma estrogen level by inactivating or inhibiting the aromatase [111]. The presence of hormone-induced tumors, including stimulation of the estrogen receptor, has been reported in about one-third of postmenopausal breast cancer patients [112]. In recent preclinical and clinical studies, the synthesis of estrogen receptor agonists/antagonists has gained importance in the prevention and treatment of breast cancer [113]. ER antagonists are commonly used in the treatment of postmenopausal women and hormone-induced breast tumors. Aromatase and sulfatase pathways play a role in the synthesis of estrogens formed only in peripheral tissues. The aromatase pathway ensures that the androgen precursor androstenedione, which is mainly secreted by the adrenal cortex, is converted into estrogen by the aromatase (AR) enzyme complex, while the estrone sulfatase pathway (E1-STS) provides the conversion of the aromatase-induced estrone to estrone sulfate (E1S) by sulfotransferase enzymes [114]. In breast tumors, the activity of the sulfatase enzyme is higher and leads to poor prognosis [115,116,117,118]. The E1-STS pathway is considered the main source of estrogen formation, which causes a fairly strong response in patients with ER + breast tumors [119,120,121]. This approach led to the discovery of new coumarins as STS [122,123,124,125] and AR inhibitors [126].

AI provides lowering in the level of estrogen and thus prevents breast cancer by reducing cell proliferation, which includes the inhibition of the formation of genotoxic metabolites of estrogen. Genotoxic estrogen metabolites are (i) catechol estrogens that covalently bind to DNA and induce mutations that initiate cancer; (ii) 2-hydroxyl-estradiol forming stable DNA insert; and (iii) 4-hydroxy-estradiol, a potential carcinogenic metabolite that causes 8-hydroxylation of guanine bases leading to estrogen induced indirect DNA damage [127,128,129].

Aromatase inhibitors are the standard option in postmenopausal breast cancer [130]. Previous studies have revealed that benzopyranone substrates, such as 4-benzyl-3-(4'-chlorophenyl)-7-methoxy-coumarin, are stronger competitive AI than aminoglutethimide. It has been reported that the specific interaction of this compound with AR shows a greater decrease in binding to the active site of AR and suppressed the proliferation of AR and ER positive MCF-7 breast cancer cells [126,131,132].

There is an over-expressed ER in the breast tumor cell at an early stage of cancer and during hormonal therapy [133,134]. Many antitumor agents used in treatment have non-selective effect and acute toxicity so use of these agents in the treatment is limited [135]. Conjugation of cytotoxic drug components to a carrier with selective activity to tumor tissues is an effective strategy in the development of effective antitumor drugs with a high therapeutic index [136,137,138,139,140,141]. Studies have shown that combining the cytotoxic agent with steroid hormones provides target selectivity of the conjugate and allow conjugates to accumulate in ER-rich cells as a result of improving antitumor activity and binding to ER [142,143,144,145,146].

In a study investigating the antiproliferative efficacy of new bioconjugates containing 3-substituted coumarins and estradiol, highly antiproliferative activity of compounds on noninvasive and invasive breast cancer cell lines (MDA-MB-231/ATCC and NCI/ADR-RES MDA-MB-435) has been revealed [147].

Cui et al. showed the anticancer effects of three synthesized coumarins derived from triphenylethylene (TCHs), occurring through the inhibition of angiogenesis on breast cancer cell lines. Compound TCH-5c inhibited proliferation, resulted in cell death, increased p21 protein expression to induce G0/G1 arrest and changed endothelial cell cytoskeleton organization and migration in EA.hy926 endothelial cells. In addition, this compound inhibited breast cancer cell line derived VEGF secretion, decreased breast cancer cell-induced endothelial cell tube formation in vitro and suppressed SK-BR-3 breast cancer cell-initiated tumor formation in vivo. These results have potential implications in developing new approaches against breast cancer[10,11,12]

II. DISCUSSION

Cancer is a fatal disease, which accounts 7, 6 million deaths (around 13 % of all deaths) worldwide in 2008. The number of deaths from cancer will continue to rise, with an estimated 13.1 million people dying in 2030 [15]. There are many different mechanisms how anticancer drugs can inhibit the division of cancer cells, some of them working as DNA intercalating agents, DNA cross-linking agents, topoisomerase inhibitors, cytoskeleton-disrupting agents and antimetabolites [16]. Most of the anticancer drugs kill cancer cells by triggering apoptosis in the cancer cells [17]. Apoptosis, which is the result of complex interaction between pro- and anti- apoptotic molecules, regulates the homeostasis and eliminates the damaged cells [18]. As antitumor activity of natural and synthetic coumarin derivatives have been extensively explored by many researchers [19, 20, 21, 22, 23, 24] and it has been proven that coumarins, depending on their structure, can act on various tumour cells by different mechanisms; they inhibit the telomerase enzyme, protein kinase activity and down regulating oncogene expression or induce the caspase-9-mediated apoptosis, suppress cancer cell proliferation by arresting cell cycle in G0/G1 phase, G2/M phase and affecting the p-gp of the cancer cell [15, 25]. Coumarin derivatives can possess not only cytostatic, but cytotoxic properties as well [26]. Marshall M. E. et al.(1994) showed that coumarin and 7-hydroxycoumarin can inhibited growth in human cancer cell lines [27], such as A549 (lung), ACHN (renal), H727 (lung), MCF7 (breast) and HL-60 (leukaemia) and in some clinical trials they exhibited anti-proliferative activity in prostate cancer [28], malignant melanoma [29] and renal cell carcinoma [30]. Coumarin, itself also exhibited the cytotoxic effect against Hep2 cells (human epithelial type 2) in dose dependent manner and showed some typical characteristics of apoptosis with loss of membrane microvilli, cytoplasmic hypervacualization and nuclear fragmentation [31]. Coumarins were also found to be excellent agents for treating side effects caused by radiotherapy which was demonstrated by Mahler et.al (1992) who applied a combinational therapy of coumarin/troxerutin in a protection of salivary glands and mucosa in patients undergoing radiotherapy [32]. Ovarian cancer, as a very common cause of death in women worldwide, is often diagnosed in its late stages and the major obstacle in its treatment is multi-drug resistance (MDR) where most of the patients develop a resistance to platinum based drugs or paclitaxel, chemotherapy drug used for treating ovarian cancer, breast cancer, lung cancer and Kaposi´s sarcoma [33, 34, 35]. Coumarin derivative RKS262 as an analogue of Nifurtimox, a drug that induces the cytotoxic and antitumor effects in neuroblastoma in vivo and in vitro, showed very potent activity in ovarian cancer (OVCAR-3 cells, human ovarian epithelial adenocarcinoma cell line) chemoresistant to platinum-based drugs [19]. Its structure is shown on 2 where it is visible that nitrofuran ring of Nifurtimox is replaced by 6-bromo-4- chlorocoumarin group. Lipophilic properties of modified coumarin group and hydrophilic character of 1- aminotetrahydrothiazine ring ensure that this potential drug could have good bioavailability [19]. The anticancer activity of this compound towards ovarian cancer cell lines (OVCAR-3) was exhibited by reducing the mitochondria-transmembrane-depolarization potential, regulating the mitochondrial Bcl-2 family pathway, increasing the pro-apoptotic factors Bid, Bad and Box expression and decreasing the expression of Bcl-xl and Mcl-1 Jamier et al. (2014) synthesized chalcone-coumarin derivatives and evaluated them for anticancer activity against different cancer cell lines, where compound on 3 had the highest cytotoxic activity against ovarian cancer (OVCAR) [37].

Lung cancer is characterized by two main types: small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), respectively [38]. Treatment for NSCLC often fails because of drugs insusceptibility to advanced lung cancer stages [38]. Many coumarin derivatives, natural and synthetic have proven to be excellent anticancer agents on this type of cancer. Osthole (7-methoxy-8-(3- methyl-2-butenyl)coumarin) (4), which was extracted from many therapeutic plants such as Cnidium monnieri [39] and Prangos ferulacea (L.) [40] inhibited the growth of human lung cancer (A- 549 cancer cells) by inducing G2/M arrest and apoptosis [41]. Umbelliprenin, [13,14,15] which was isolated from Ferula plant species, induced the apoptosis in QU-DB (large cell lung cancer) and A549 adenocarcinoma cell line, at different doses [20]. Wang et al. (2013) demonstrated that naturally extracted 7,8 –dihydroxycoumarin (daphnetin) (4) inhibits the proliferation of A549 human lung adenocarcinoma cells and by suppression of Akt/NF-κ B signalling pathways induces the apoptosis in concentration dependent manner [17]. Musa et al. (2012) found that some of the coumarin-based benzopyranone derivatives induced apoptosis in human lung cancer (A549) by a different mechanisms. Coumarin derivative on 5a. induces the apoptosis by increasing the expression of pro-apoptotic Bax and decreasing anti-apoptotic Bcl-2 expression. However, coumarinbenzopyranone derivative on 5b. decreased an expression of both Bax and Bcl-2 proteins [38].

III. RESULTS

Musa et al. (2015) also investigated in vitro antitumor activity of some 3-arylcoumarin derivatives in A549 cancer cell lines (lung cancer). The most active compound was 8–(acetyloxy)-3-(4-methanesulfonyl phenyl)-2-oxo-2Hchromen-7-yl acetate (6), a compound which showed selective cytotoxicity, causing cell arrest in S phase of the cell cycle which is the indication of inhibiting DNA synthesis in cells, loss of MMP (matrix metalloproteinase) and increase of ROS (reactive oxygen species) production in A549 cancer cell lines [21]. Among synthesized iodinated-4-aryloxymethylcoumarins improved anti-cancer activity against A-549 (human lung cancer) was observed in compounds having clorine at position 6 and 7 and bromine at position 6 of coumarin ring

Hybrid molecules which consist of substituted trans-vinylbenzene moiety on coumarin scaffold were synthesized by Belluti et al. (2010) [43]. The most promising results, with an excellent antiproliferative and proapoptotic activities were 7-methoxycoumarin nucleus with 3,5- disubstitution pattern of the trans-vinylbenzene moiety. Compound on 8a. 4-[(E)-2-(2,4-dimethoxyphenyl)ethenyl]-7-methoxy-2H-chromen-2-one administered orally at dose of 10- 20 mg/kg in patients with lung carcinoma (H460) inhibited growth of cancer cells, without a toxic effects[16,17,18]

Hormone oestrogen has the crucial role in development of the breast cancer, the most frequent malignant disease in women, therefore many therapies are designed to block his activity [46]. Cinnamoyl-coumarin derivatives were especially effective in oestrogen-dependent cancers, such as breast (MCF7) and ovarian (OVCAR) cancer cell lines, the most potent . These compounds are selective nonsteroidal inhibitors of 14 β-hydroxysteroid dehydrogenase type 1, an enzyme that catalyses NADPH-dependent reduction of the weak oestrogen, oestrone, into the most potent oestrogen, oestradiol [37].

Tamoxifen (TAM) as non-steroidal triphenylethylene derivative is the most widely used selective oestrogen receptor modulator (SERM), [48] but usually a drug resistance develops through couple of years of treatment in patients [46]. Therefore, Sashidhara et.al. (2013) developed a new hybrid molecules coumarin – monastrol, where compound on the 13. showed the most potent selective activity against breast cancer cell lines MCF-7 and MDA–MB-231. This compound induced caspase-3 activation and apoptosis and caused arrest of MCF-7 cell cycle at G1 phase [46].

Cancers of the gastrointestinal (GI) tract are often life-threatening malignancies, which can be a severe burden to the health care system. Globally, the mortality rate from gastrointestinal tumors has been increasing due to the lack of adequate diagnostic, prognostic, and therapeutic measures to combat these tumors. Coumarin is a natural product with remarkable antitumor activity, and it is widely found in various natural plant sources. Researchers have explored coumarin and its related derivatives to investigate their antitumor activity, and the potential molecular mechanisms involved. These mechanisms include hormone antagonists, alkylating agents, inhibitors of angiogenesis, inhibitors of topoisomerase, inducers of apoptosis, agents with antimitotic activity, telomerase inhibitors, inhibitors of human carbonic anhydrase, as well as other potential mechanisms. Consequently, drug design and discovery scientists and medicinal chemists have collaborated to identify new coumarin-related agents in order to produce more effective antitumor drugs against GI cancers.

Coumarins are currently categorized into four distinct classes: pyranocoumarins, furanocoumarines, simple coumarins, and coumarins with pyrone-substituents (34). Simple coumarins include alkoxylated, alkylated, and hydroxylated–derivatives of coumarin, and associated glycosides, such as skimmin, umbelliferone, esculetin, herniarin, limettin, esculin, daphnin, and daphnetin (34). Furanocoumarins contain a furan ring bound to the coumarin ring. Furanocoumarins can be categorized into two groups based on the ring fusion sites: linear furanocoumarins attached at C6/C7 and angular furanocoumarins attached at C7/C8. Psoralen, imperatorin, and xanthotoxin are linear furanocoumarines, while bergapten, isobergapten, pimpinellin, isopimpinellin, and angelicin are examples of angular furanocoumarins (34–37). Pyranocoumarins have a 6-membered pyran ring attached to the benzene ring at C7–8 (angular) or C6-7 (linear). Seselin, visnadin, and xanthyletin are examples of pyranocoumarins (38, 39). Coumarins with pyrone-substituents are divided into three different groups: 3-phenylcoumarin (gravelliferone and coumestrol); 4-hydroxycoumarin (icumarol and novobiocin), and 3,4-benzocoumarin (alternariol). Plants do not contain 4-hydroxycoumarins in their natural state. Warfarin is also a synthetic compound belonging to this family (36, 40).

Coumarin compounds with multiple biological targets have been recently identified, and these could be used as new therapeutic agents to treat disorders, such as congestive heart failure and cancer. Naturally occurring drugs have become popular, since they are relatively cheap, have low toxicity, do not cause the development of resistance, as well as having significant efficacy (41, 42). Consequently, novel compounds extracted from plants and microorganisms can be combined with current chemotherapeutic drugs for cancer treatment (43). Coumarins are a large family of natural agents with diverse pharmacological properties. These compounds are currently extracted from a wide range of plants,

such as Artemisia, Achillea, and Fraxinus genera, but they can also be synthesized in the laboratory using standard chemical reactions. Various techniques, including reflux, maceration, ultrasonic-mediated, and microwaves, have been used to extract and purify coumarin derivatives from plant source material. In the laboratory, organic reactions such as Von Pechmann, Perkin, Wittig, and Knoevenagel have been used to synthesize coumarins (42). The shikimic acid pathway plays a pivotal role in coumarin biosynthesis in nature. The shikimic pathway consists of a series of enzymatic reactions resulting in the production of umbelliferone, chorismic acid, p-coumaric acid, and cinnamic acid. In addition, the enzyme cytochrome P450 plays a major role in converting cinnamic acid into isofraxidin, umbelliferone and scopoletin through an ortho-hydroxylation reaction (42, 44).

It is well known that many cancers can recur after being treated with conventional chemotherapy. This phenomenon is known as multidrug resistance (MDR), which is often due to up-regulation of transmembrane protein drug-efflux pumps, including p-glycoprotein (P-gp) also known as ATP-binding cassette sub-family B member 1 (ABCB1), or multidrug resistance-associated protein 2 (MRP2, ABCC2) which can actively pump many anti-cancer drugs out of the cells, a process powered by ATP hydrolysis. In this context, coumarins have the potential to decrease the activity of MRP2 and P-gp, and could overcome MDR.

Baghdadi et al. (45) isolated six coumarin derivatives, including mansorin-I, mansorin-II, mansorin-III, mansorin-A, mansorin-B, and mansorin-C, from Mansonia gagei a plant of the Stercullariaceae heartwood family. Their study showed that these agents had promising antitumor activity against hepatocellular carcinoma, breast cancer, colorectal cancer, and cervical cancer cell lines. In this context, mansorin-II and mansorin-III had the highest antitumor effect, with a half-maximal inhibitory concentration (IC50) of 3.95-35.3 µM and 0.74 -36 µM, respectively. Moreover, mansorin-II was able to potentiate the antitumor effects of taxol. This effect occurred partly by inhibiting the P-gp efflux activity.[19]

Carbonic anhydrase is a zinc-containing metalloenzyme, responsible for catalyzing the reaction between carbon dioxide and water to produce carbonic acid, bicarbonate, and hydrogen ions. This reaction maintains the balance between the intracellular and extracellular pH at stable levels, and allows the transfer of ions through the transmembrane space, and other metabolic processes to proceed (46). Sixteen different carbonic anhydrase enzymes have been identified. Of these, CA I and CA II are cytoplasmic enzymes, while CA IX and CA XII are transmembrane proteases. Because cancer cells and their surrounding microenvironment exist in a state of hypoxia, they increase their rate of glycolysis to satisfy their metabolic requirements, and therefore lactic acid accumulates in the tumor microenvironment. CA XII and CA IX are up-regulated in tumor cells dur to the action of HIF (hypoxia-inducible transcription factor). Carbonic anhydrase enzyme plays a role in the growth and metastatic dissemination of primary tumors, as well as the development of resistance to chemotherapy (46, 47).

CA IX and CA XII are highly expressed in many cancer types, and may be promising targets for therapeutic intervention. Belma et al. (48) investigated a wide range of compounds for their inhibitory effect on CA XII, CA IX, CA II, and CA I enzymes in colorectal cancer cells. They found that some compounds could effectively inhibit both CA XII and CA IX. The most active was 4-((((2-((1-(3-((2-oxo-2H-chromen-7-yl)oxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-methylene)amino)methyl)benzenesulfonamide, which could selectively inhibit proliferation in colorectal cancer cells, and had an inhibitory constant (Ki) of about 596.6 nM for CA XII and 45.5 nM for CA IX.

The caspase family of enzymes are involved in the induction of apoptosis. These enzymes include caspase-10, 9, 8, 7, 6, 3, and 2. Among these, caspase-10, 9, 8, and 2 are involved in the initiation of apoptosis. Caspase-2 catalyzes its own cleavage and becomes activated to trigger apoptosis under the influence of intracellular signaling. Subsequently, the process of apoptosis is executed by caspase-7, -6, and -3, which are activated by upstream promoters. These caspases cleave various functional and structural proteins, especially PARP (poly-ADP-ribose polymerase) (49). Bcl-2 (B cell lymphoma-2) is a major tumor-promoter gene that generally inhibits cellular apoptosis. The Bcl-2 family contains proteins with both anti-apoptosis and pro-apoptosis activity. PUMA, Bax, and Bad are examples of pro-apoptotic proteins which are predominantly found in the cytoplasm. After being activated by apoptosis signaling, these proteins migrate to the mitochondrial outer membrane, where they form transmembrane channels that allow the mitochondria to expel cytochrome C, thus activating caspases resulting in apoptosis. On the other hand, the Bcl-2 family also contains proteins with anti-apoptotic properties, primarily found in the mitochondrial outer membrane, which can inhibit apoptosis by preventing loss of cytochrome C from the mitochondria (49). Coumarin-derived compounds can modulate the expression of pro-apoptotic proteins and could thus help to treat malignant tumors.

Nordin et al. (50) extracted a coumarin compound known as PulchrinA, from a Malaysian plant called Enicosanthellum pulchrum in the Annonaceae family. They evaluated the potential of this coumarin-derived agent to produce apoptosis

in ovarian tumor cells. Pulchrin A was found to reduce Bcl-2 expression and increase Bax protein expression via increasing caspase-9 and caspase-3 activity, with an IC50 level about 22 μM in ovarian cancer cells.

The phosphatidylinositol kinase PI3K is found in the intracellular compartment. PI3K can activate other protein kinases such as PKC, PKB, and PKA, and plays a pivotal role in processes, such as cell differentiation, growth, migration and apoptosis. AKT or PKB is a serine/threonine kinase, which is a downstream target for PI3K, and is significantly correlated with cellular proliferation and apoptosis. In addition, AKT activates CDK2 and CDK4 and modulates p27, and acts as a cyclin-dependent kinase inhibitor, thereby preventing cell cycle progression. AKT also has anti-apoptotic activity by acting on several pathways. Some examples of the anti-apoptotic activity of AKT include, inhibiting caspases and Bax, inhibiting GSK3 activity (which increases apoptosis through cleavage of the cytoskeleton protein β-catenin), as well as reducing the adhesion of cells. AKT can increase the activity of transcription factor NF-κB which in turn leads to increased repair of DNA damage, reducing pro-apoptotic FasL gene expression, and inhibiting the release of cytochrome C out of the mitochondria. mTOR is another threonine/serine kinase, which is a downstream target of AKT. Following its own activation, mTOR activates the ribosomal proteins p70S6K and E-BP1 (a translation inhibitor) (4). The binding of 4E-BP1 to eIF-4E becomes weaker upon phosphorylation; as a result the free eIF-4E is able to bind to other factors to initiate protein translation.

After being activated, p70S6K can increase protein production. The PI3K/AKT/mTOR pathway plays a crucial role in the modulation of the cell cycle, cell viability, proliferation, differentiation, and metastasis (51, 52). This signaling pathway has been shown to be correlated with human carcinogenesis. Abnormal up-regulation of this signaling pathway has a role in the formation, growth, progression, and chemoresistance of cancer cells, and could be a new potential therapeutic target for cancer treatment (53, 54). 5-Methoxypsoralen is a linear furocoumarin (psoralen) extracted from plant sources (such as parsley and bergamot) by alkali treatment. In a study by Guo et al. (55), 5-methoxypsoralen was found to inhibit PI3K, mTOR, and Akt phosphorylation and expression in human glioma cells, resulting in the inhibition of the PI3K/Akt/mTOR signaling axis. Following exposure to 5-methoxypsoralen, the DNA in glioma cells was damaged by fragmentation, and abundant autophagic vacuoles were formed.

Microtubules are an important constituent of the cell cytoskeleton, and control cell cycle progression, proliferation, cell morphology, and intracellular signaling. Several anticancer drugs can cause microtubule depolymerization, or else they block microtubule aggregation, resulting in cell cycle arrest at the M-phase, and thus mitosis is blocked in tumor cells. Microtubules have three different binding sites for the anticancer drugs, vincristine, paclitaxel, and colchicine. Therefore paclitaxel, vincristine, and colchicine are often used to inhibit microtubules. Moreover, these drugs are substrates of efflux systems mediated by P-gp pumps, resulting in multidrug resistance in cancer cells. A study by Dahong evaluated the effects of the coumarin derivative, Ferulin C on proliferation in breast cancer in vitro and in vivo. Ferulin C is a coumarin isolated from the roots of Ferula ferulaeoides, which can also bind to colchicine binding sites on β-tubulin, thus preventing its aggregation. Ferulin C can inhibit the polymerization of tubulin (IC50 = 9.2 μM) compared to colchicine (IC50 = 1.8 μM) used as the reference. Ferulin C was found to specifically alter the microtubule structure without affecting tubulin expression. Ferulin C destablilized microtubules, and increased the activity of p21, while it suppressed PAK1. Higher levels of PAK1 are correlated with unfavorable outcomes, while higher levels of p21 are correlated with favorable outcomes in patients with breast cancer.

Ferulin C caused cell cycle arrest at the G1/S phase by activating the p21Cip1/Waf1-CDK2 signaling axis. A xenograft model of breast tumor was used in an in vivo study by Dahong, where they assessed the anti-cancer effects of Ferulin C (low dose, 25 mg/kg; median dose, 50 mg/kg; high dose, 100 mg/kg). Their study showed that Ferulin C could block breast tumor cell proliferation in the xenograft model, and this anti-cancer activity correlated with the in vitro results (56).

Coumarins and Gastric Cancer

Gastric cancer (GC) is among the most prevalent GI tumors globally. Approximately 1 million patients are newly diagnosed with gastric carcinoma each year. Because of its aggressiveness, gastric cancer is the third cause of cancer-related death (57). However, the conventional drugs are limited by unwanted toxicity and adverse side effects due to their poor selectivity for cancer cells compared to normal mammalian cells (58). Consequently, identifying novel therapeutic agents with lower toxicity is needed for more successful management of patients with gastric cancer.

Molecular hybridization is a novel concept in drug development and discovery. It is based on combining two or more biologically active molecules by attaching them together using appropriate covalent bonds. Compared to their individual elements, the hybridized structures show superior or novel biological functions (59).

Nucleotides are nitrogen-containing heterocyclic structures that are basic components of RNA and DNA (60, 61). Because nucleobases play major roles in various cellular processes, nucleotides are often utilized as pharmacophores, especially in antitumor drugs (62–64). Interestingly, nucleobases can show in vitro cytotoxicity in a variety of human tumor cell lines (64) caused by several mechanisms. The click reaction is an easy synthetic approach to prepare the triazole scaffold (a nitrogen containing heterocyclic compound) frequently used as a linker in pharmaceutical research (65). Furthermore, the use of 1,2,3-triazole is associated with increased solubility (66), improved strength of binding to other biological compounds, and can show synergistic effects on biological functions (67). Considering their specific rigid structure and binding to particular hormone receptors, steroids are a major family of biological compounds, widely used in drug design (68). Modification of the C-16 atom in steroids can be used to attach other moieties, in order to produce tumor-targeted cytotoxic agents (69–73).

Using the molecular hybridization technique, Zhao et al. prepared a group of analogues of the 1,4-disubstitued 1,2,3-triazole-nucleobase, including additional moieties such as steroids, coumarins, or quinolines (74). In their study, a number of these compounds were shown to suppress the cellular proliferation of tumor cells. In this context, compound 20c showed an anti-proliferative activity in SGC-7901 cells (IC50 = 2.28 μM) and MGC-803 cells (IC50 = 1.48 μM) and did not affect healthy non-cancerous cells. Compound 20c may inhibit TGF β1 expression in gastric cancer cell lines, and suppress cellular invasion and migration. Compound 20c could be used as a novel skeleton for therapeutic agents against GC with minimal side effects (74).

ISOIM (isoimperatorin) is a member of the 6,7-furanocoumarin family and is isolated from plants in the umbelliferae family, including Heracleum maximum, Angelica dahurica, Peucedanum ostruthium. Chinese angelica has been frequently utilized in ancient Chinese medicine (75). Isoimperatorin is a secondary plant metabolite with numerous pharmacological properties, such as anti-hypertensive, analgesic, anti-inflammatory, antitumor, antiviral, and antibacterial activity (76–80). In addition, ISOIM can inhibit proliferation in several cancer cell lines, including skin cancer SK-MEL-2, ovarian cancer SK-OV-3, lung cancer A549, breast cancer MCF-7, glioblastoma XF498, and colon cancer HCT-15 (76–81). ISOIM was found to suppress the proliferation of SGC-7901 gastric cancer cells and modify the expression of several anti- and pro-apoptotic proteins (82).

In a study by Yang et al., the pro-apoptotic and anti-proliferation properties of ISOIM in BGC-823 gastric cancer cells were evaluated, along with the potential biological mechanisms (83). The MTT assay measured cellular proliferation, while hematoxylin and eosin staining, acridine orange/ethidium bromide staining, and Hoechst 33258 were employed to assess cell morphology. Flow cytometry assays measured apoptosis and cell cycle status, and the expression level of pro-apoptotic proteins was evaluated using Western blotting. It was found that ISOIM could suppress proliferation through inducing cell cycle arrest at the G2/M stage. Moreover, ISOIM induced apoptosis through increased expression of Bax (Bcl-2-associated X) and reduced expression of Bcl-2, thus reducing the Bcl-2/Bax ratio compared to the control cells. Furthermore, the administration of ISOIM led to cytochrome c release from the mitochondria into the cytosol, along with activation of caspase-3, indicating that apoptosis was stimulated by the mitochondrial pathway in BGC-823 cells (83).

Perumalsamy et al. performed an in silico and in vitro study to investigate whether SSBC (styrene substituted biscoumarin) could induce apoptosis and inhibit proliferation of tumor cells (84). The MTT assay was used to measure proliferation in gastric cancer (AGS) cell lines in addition to healthy lung cell lines (MRC-5 and L-132). Molecular docking was used to examine the binding between SSBC and Bcl2. Moreover, PASS (spectrum prediction analysis) was used to evaluate the biological effects, and ADME was used to measure pharmacological properties and drug likeliness. DAPI/PI staining, Hoechst staining, and FACS were employed to evaluate SSBC-induced apoptosis in AGS cells. Western blotting and Quantitative Real-Time Reverse Transcription (qRT-PCR) were used to investigate the mechanisms of apoptosis induction. The IC50 values of SSBC for MRC-5 and L-132 cells were 285 and 268 μg/mL, respectively, while for AGS cells the IC50 was 4.56 μg/mL. In silico analysis predicted that SSBC could bind to the BH3 domain of anti-apoptotic proteins, which could then activate apoptosis and cell death. Using ADME predicted that SSBC had a high binding affinity (~ 99.08%) and a high absorption rate (~95.57%) in the small intestine. The PASS software suggested that SSBC could affect the expression level of several proteins involved in apoptosis. Western blotting, FACS, DAPI/PI staining, qRT-PCR, and Hoechst staining confirmed apoptosis in AGS cells. SSBC may be particularly effective to trigger apoptosis mediated by the intrinsic pathway, and thus in vivo studies and human clinical trials for GC may be justified (84).

Farnesiferol C (FC) is a member of the coumarin family, belonging to the sesquiterpene group, which is routinely extracted from Ferula szowitziana DC roots (85). Apiaceae (genus Ferula) are plants that are widely distributed in Northern Africa, Central Asia, and the Mediterranean region (86), and these plants are a rich source of natural compounds, including coumarins and sesquiterpenes (87). FC has a variety of biological functions, including anti-

tumor activity in vitro and in vivo, reducing the formation of new blood vessels, and also shows activity against Leishmania infection (88). Nevertheless, FC has poor solubility, and relatively low bioavailability both in vivo and in vitro, which hinders its potential therapeutic applications (89). However, recent studies have shown that FC solubility and antiproliferative effects against cancer cells may be improved by incorporation into dendrosome nanoparticles. Dendrosomes are spherical, covalently linked, degradable, neutral, and self-assembled nanoparticles which have become popular for their ability to deliver herbal agents and genes into various cell lines (89–93).

Aas et al. performed a study to determine the potential antitumor effects on AGS cells of DFC (dendrosomal farnesiferol C) (94). RT-PCR was used to assess the Bax/Bcl-2 ratio in order to determine apoptosis. MTT assay was used to evaluate the antiproliferative effects of DFC. DFC inhibited AGS proliferation in a time- and dose-dependent manner, compared to free FC. DFC increased the Bcl-2/Bax expression ratio in AGS cells. Taken together, the nano-formulated farnesiferol C may be useful in tumor-targeted therapy

IV. CONCLUSION

Coumarin compounds have a broad range of biological activity, and consequently for decades many scientists have investigated these compounds, and some have devised new related structures to potentially treat cancer, as well as a plethora of other diseases. Coumarins play a crucial role in numerous biological processes such as antioxidant systems, regulation of cell growth, and chemoprevention from various disorders. Coumarin compounds have anti-cancer activity by regulating cell differentiation, growth, and the immune system responses. Therefore, coumarins can be combined with conventional drugs, to produce novel antitumor treatments with higher efficacy and fewer adverse effects.

Various synthetic methods such as the Knoevenagel, Pechmann, Perkin, Wittig, and Claisen reactions have been used to prepare coumarins as well as a diverse range of derivatives. Thanks to theses new molecular manipulation techniques, analogs with more potent activity and a higher therapeutic index have been discovered, even though coumarin itself and some of its natural compounds may show hepatotoxicity, which may limit their clinical use. Recent studies have shown that the antitumor effects of coumarins may be increased by the addition of various substituents to specific areas of the coumarin structure. As a result, this approach has led to the identification of some novel antitumor compounds.

Moreover, both synthetic and natural coumarins have been found to modulate specific signaling pathways, providing mechanistic explanations for their antitumor activity. Coumarin and its derivatives have promising antitumor properties and may result in novel antitumor drug regimens, however further laboratory studies are required before large scale clinical trials can be undertaken.[20]

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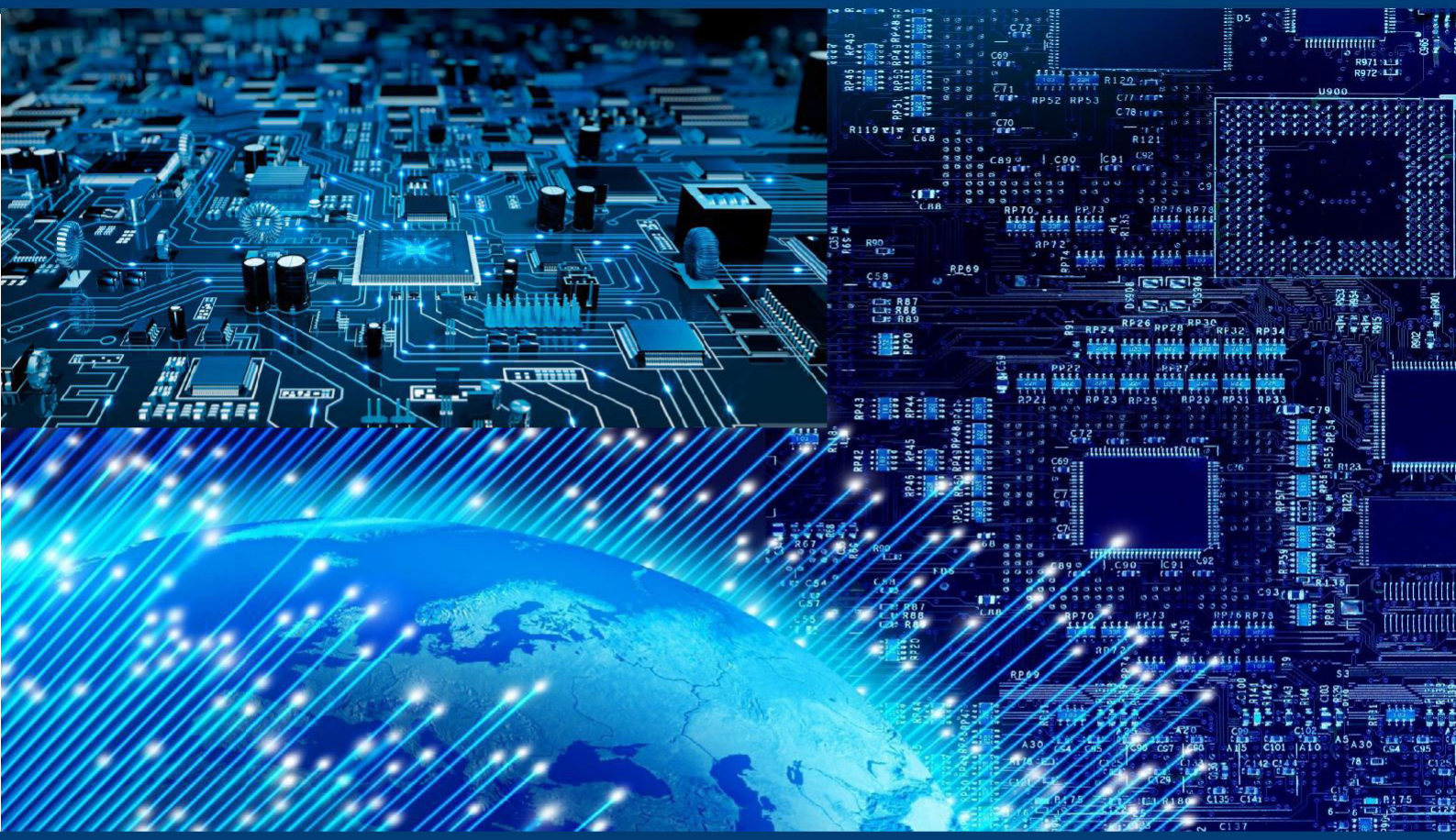

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