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BIOLOGICAL ACTIVITY OF QUINONES

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ABSTRACT: Quinones constitute a structurally diverse class of phenolic compounds with a wide range of pharmacologial properties, which are the basis for different applications in the broad field of pharmacy and medicine. In traditional medicine all over the world, plants which are rich in quinones are used for the treatment of a variety of diseases. Besides the classical applications of these plants in industry (dyestuffs) and pharmaceutical (laxatives) practice, the relatively new field of biologically active quinones will be discussed. This review gives an account of the work done on naturally occurring bioactive quinones from 1992 to the present date. The biological activity detected in quinones from natural and synthetic sources has been discussed in relation to chemical structure under the respective titles.

INTRODUCTION

Long before anything was known of their chemistry, rhubarb, aloes, senna and cascara were recognized as forming a natural group of laxative drugs. Moreover certain vegetable and animal dyestuffs such as madder and cochineal were of great economic importance before the introduction of synthetic dyestuffs. Later the chemical similarity of these laxative drugs and dyestuffs became apparent. The establishment of the common basic structural pattern (a *para-* or an *ortho-* substituted dione in conjugation with the doble bonds of a benzene or condensed aromatic ring system) provided the basis for the systematic chemical recognition and identification of quinones from natural sources. Knowledge of comparative taxonomy, biological actions and ecological interactions has greatly contributed to the discovery of new quinones.

In traditional medicine all over the world, plants which are rich in quinones are used for the treatment of a variety of diseases. The biological

activity of quinones has prompted several pharmacological studies in order to ascertain their possible use in medicine. This review gives an account of the work done on bioactive quinones from 1992 to the present date. The biological activity detected in quinones from natural and synthetic sources has been discussed in relation to chemical structure under the respective titles. Information on novel quinones and new plant sources of quinones is also updated. A separate section deals with quinone production in plant cell and tissue cultures, since cultured plant cells have proven to be a very useful tool in biosynthesis studies. Cell cultures also occasionally accumulate new metabolites which are not found in the parent plants.

OCCURRENCE AND STRUCTURAL CHARACTERISTICS

Quinones are found in bacteria, fungi, lichens, Gymnosperms and Angiosperms [1-7]. In the animal kingdom, quinones occur in echinoderms, e.g. isoprenoid quinones in sea urchins [8] and arthropods, e.g. anthraquinones in insects such as cochineal [9,10]. Plastoquinones, α-tocopherolquinones and phylloquinone are primary metabolites, probably present in all photosynthesising tissues, whereas ubiquinones have been found in most plants, and generally in animals. The majority of quinones found in plants are relatively simple benzoquinones, naphthoquinones or anthraquinones, although less common skeletal structures are also found to occur, such as terpenoid quinones and higher polycyclic quinones. Most quinones found in nature are *p*-quinones, but *o*-quinones also exist.

In higher plants, anthraquinones are found in the Rubiaceae, Leguminoseae, Rhamnaceae, Polygonaceae, Liliaceae and Scrophulariaceae. Most naphthoquinones occur in Bignonaceae, Verbenaceae, Juglandaceae, Plumbaginaceae, Borraginaceae, Lythraceae, Balsaminaceae, Ebenaceae and Droseraceae. Myrsinaceae and Borraginaceae are some families in which benzoquinones are found to accumulate.

LAXATIVE ACTIVITY

The anthranoid compounds, which can be chemically described as dihydroxy-anthraquinones, -dianthrones and –anthrones, possess a laxative

effect. As these substances are the constituents of some plants and their extracts (aloe, cascara, frangula, rhubarb and senna) they are often referred to as vegetable laxatives. Because of their chemical structure, they are carried unabsorbed to the large bowel, where metabolism to active aglycones takes place. The active aglycon is released by bacterial hydrolysis of the sugar. The intestinal bacterial flora also accounts for the reduction of anthraquinone aglycons to the corresponding anthrones [11-13]. These aglycones exert their laxative effect by damaging epithelial cells, which leads directly and indirectly to changes in absorption, secretion and motility. After adsorption, the anthranoids are transformed mainly to their corresponding glucuronide and sulfate derivatives, which appear in urine and bile. However, chronic abuse of anthranoid laxatives has recently been associated with an increased risk of colorectal carcinoma, as we will see.

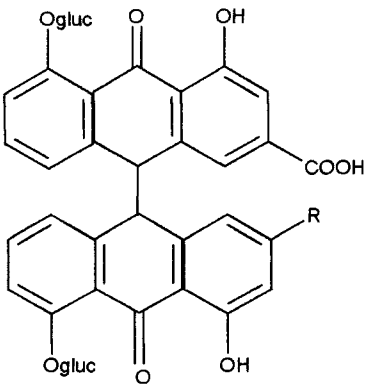

Fig. (1). Structure of sennosides

Several studies have been conducted in order to establish and better understand the mode of action of anthranoid laxatives. For example, Lemli [14] presented a review of the study of the mode of action of sennosides, Fig. **(1)** the active constituents of the senna drug. An interaction between rhein-anthrone, the active metabolite of sennosides, and the immune cells of the colon is suggested as a base for laxative activity. Several studies aimed to

explore the mechanism involved in the synergistic purgative actions of rhein-anthrone and aloe-emodin-anthrone, another active metabolite of sennosides.

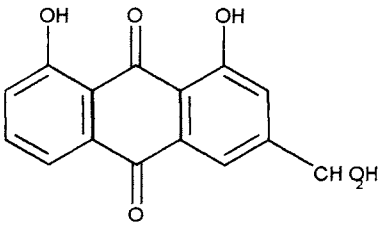

Fig. (2). Structure of aloe-emodin

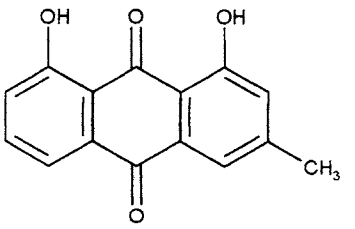

Fig. (3). Structure of crisophanol

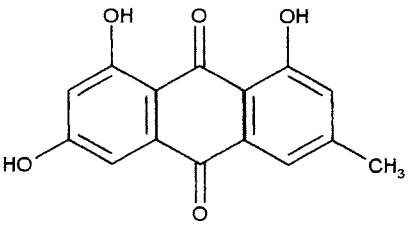

Fig. (4). Structure of emodin

This synergistic effect in mice results from synergistic stimulation of large intestinal transit and large intestinal water secretion [15,16]. Recently, several investigations have been performed to determine whether intracaecally administered rhein-anthrone and anthraquinones such as aloe-emodin, Fig.

(2), chrysophanol, Fig. **(3)**, emodin, Fig. **(4)** or rhein, Fig. **(5)** synergistically enhance purgative action, as has been observed for rhein-anthrone and aloe-emodin-anthrone. These results confirmed that rhein-anthrone and aloe-emodin synergistically exert a purgative action [17].

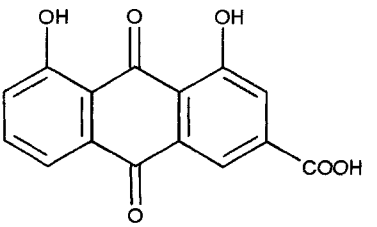

Fig. (5). Structure of rhein

Kuo *et al.*, [18] investigated the structure-activity relationships of anthraquinones on intestinal motility, using rabbit small intestinal strips. This study revealed the critical requirement of a hydroxy group at 2 position, whereas the presence of other polar groups at this position, such as an amino, aldehyde and carboxylic acid groups, significantly reduced the activity. The presence of a methyl group and esterification of the carboxylic acid at 2 position was found to abolish the activity.

ANTINEOPLASTIC ACTIVITY

Folk medicine has attributed antitumor properties to preparations from medicinal plants containing quinones. Quinones for the anthraquinone, naphtoquinone and benzoquinone group were studied for their inhibitory growth effect on cultured malignant cells, which include cultured ovarian, breast, prostate, melanoma, lung, colon and pancreatic cancer cells.

For example, emodin, Fig. **(4)** is an active component from the root and rhizome of *Rheum palmatum* L. that has been reported to exhibit antitumor effects, but the mechanism is not known. Several studies demonstrated that emodin induces cell apoptosis in human lung squamous carcinoma cell line

CH27 and on cells derived from human colon carcinoma [19-22]. *Rheum officinale* H. Bn., a Chinese medicinal plant, also contained large amounts of anthraquinones as active compounds, such as emodin, Fig. **(4)**, chrysophanol, Fig. **(3)** and rhein, Fig. **(5)**, which specifically inhibited one of the carcinogenesis-related enzymes (cytochrome P450) [23]. Additionally, chrysophanol, emodin and rhein have been shown to inhibit benzo(α)pyrene-mediated DNA damage in human hepatoma cell line Hep62. In the same way, Kuo *et al.* [24] tested four anthaquinones purified from another Chinese herb *Polygonum hypoleucum* Onwi (emodin, Fig. **(4)**, emodin-1-glucoside, physcion, Fig. **(6)** and physcion-1-glucoside) for their effects on human mesangial cell proliferation *in vitro*. On a percentage basis, emodin had the highest suppressing activity on cells proliferation.

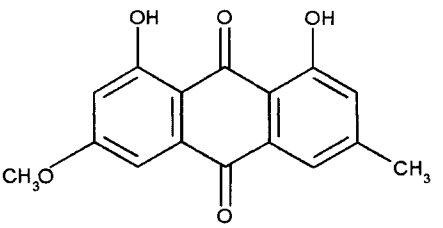

Fig. (6). Structure of physcion

Another natural anthraquinone, aloe-emodin, Fig. **(2)** present in *Aloe vera* L. leaves, has a specific *in vitro* and *in vivo* antineuroectodermal tumor activity. Aloe-emodin has been reported to be non-toxic for normal cells, but to possess specific toxicity for neuroectodermal tumor cells. Taking into account its unique cytotoxicity profile and mode of action, aloe-emodin might represent a conceptually new lead antitumor drug [25]. More recently, a free-floating cell line has been established from a metastatic lesion of a Merkel cell carcinoma patient. The cell line was characterized by immunocytochemical reactions with antibodies against the epithelial and neuroendocrine antigens. Aloe-emodin significantly inhibited the growth of Merkel carcinoma cells, meriting further investigation as a potential agent for treating these tumors [26].

Previously, Grimaudo *et al.* [27] had studied the effects of five purified anthraquinones from this plant on human K562 leukaemia, and only aloe-emodin, Fig. **(2)** produced reproducible antitumor effects. Research on the antitumor activity of compounds extracted from *Aloe vera* probably deserves to be continued. Shimpo *et al.* [28] examined the modifying effect of the whole leaf of another species of this genus, *Aloe arborescens* Miller var. *nathalensis* Berger on azoxymethane-induced aberrant crypt foci, putative pre-neoplastic lesions in the rat colorectum, suggesting that this plant has a chemopreventive effect against colon carcinogenesis, at least in the initiation stage.

Several studies demonstrated that aloin, another natural anthraquinone with potential antitumor activity, was effective on mice bearing solid Erlich carcinoma [29-31]. The antitumor activity of aloin was also examined against two epithelial-type tumor cell lines: breast and ovarian [32]. Other natural anthraquinones isolated from the roots of *Morinda elliptica* Ridl. were assayed for their cytotoxic activities. Of these, only damnacanthal was very cytotoxic against the breast carcinoma MCF-7 and T-lymphoblastic leukaemia CEM-SS cell lines [33].

The number of hydroxy groups in the anthraquinone nucleus seemed to play an important role in the degree of cell growth inhibition. Anthraquinones with two or three hydroxy groups were more effective than those with no hydroxy groups such as 9,10-dioxoanthracene [19]. Edenharder *et al.* [34] demonstrated that several anthraquinones and structurally related monoketonic compounds inhibited mutagenicity induced by 2-amino-3-methylimidazol[4,5-f]-quinoline in *Salmonella typhimurium* TA 98. A carbonyl function was a prerequisite for antimutagenicity, while, in general, anthraquinones were more potent antimutagens than structurally-related monoketonic compounds.

A series of anthraquinones has been chemically synthethized and the influences of structural features, such as the different functionalities in the nucleus have been studied in relation to cytotoxicity toward neoplastic cells. 1,3-dihydroxy-9,10-anthraquinone synthetic derivatives were tested *in vitro* for inhibition against several different human cancer cell lines. Structure-activity analysis indicates that epoxidation of the hydroxyanthraquinone increased cytotoxicity against tumor cells, but ring-opening of the epoxide

group with amine did not enhance cytotoxic activity [35]. In the same way, 2-(1-hydroxyalkyl)-1,4-dihydroxy-9,10-anthraquinone derivatives were chemically prepared and tested for their antitumor activity. Some of them showed remarkable activity [36]. Additionally, novel esters of chlorambucil with 2-(1-hydroxyalkyl)-1,4-dihydroxy-9,10-anthraquinone were synthesized and tested for their antitumor activity in mice bearing S-180 ascitic cells, as well as for cytotoxic activity against L1210 cells. Eight of them were highly cytotoxic [37].

The amino-substituted anthracene-9,10-dione derivatives also represent one of the most important classes of potential antitumor agents [38]. Recently, Zagotto *et al.* [39] have synthesized a new class of D- and L-aminoacyl-anthraquinone derivatives, and have tested these new compounds as cytotoxic agents. These studies have correlated their activity with the configuration of the chiral aminoacyl moiety [40,41]. Molecular modelling has been carried out for a number of amine-functionalised anthraquinone derivatives to determine the extent of their binding to DNA and their ability to inhibit the enzyme telomerase. The findings suggest that anthraquinone derivatives of this type inhibit telomerase [42,43].

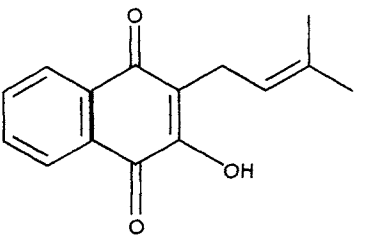

Fig. (7). Structure of lapachone

Naturally-occurring quinones of the naphthoquinone group also exert potent antineosplastic activity, and it is interesting highlight that the most studied compound is lapachone, Fig. (7). Pyranonaphthoquinones such as α- and β-lapachone have diverse biological activities and there has recently also been an increased interest in their anticancer activity. β-Lapachone, a plant

product obtained from plants of the *Tabebuia* genus, has been shown to be a novel inhibitor of DNA topoisomerase I, with a different mode of action from camptothecin and a chemical structure distinct from those of current anticancer drugs [44,45]. β-Lapachone has been found to induce apoptosis in various human cancer cells. Several studies demonstrated that β-lapachone induces cell death with the characteristics of apoptosis in human and rat prostate cancer cell lines [46,47]. This effect of β-lapachone was also observed in human promyelocytic leukaemia cell line HL-60 [48] and human multiple myeloma cell lines [49]. Weller *et al.* [50] also find that β-lapachone is much more potent than camphothecin in inducing acute cytotoxic effect on human malignant glioma cells. Among other human carcinoma and adenoma cell lines tested, human breast and ovary carcinoma [51], human hepatoma cell line HepA2 [52] and nasopharyngeal tumor cells KB [53] showed sensitivity to the cytotoxic effect of β-lapachone. These results suggest that β-lapachone is a potential compound to be added to cancer chemotherapy, particularly for prostate cancer. In addition, ablation of tumor colonies was seen in a wide spectrum of human carcinoma cells in culture after treatment with the combination of β-lapachone and taxol. This combination therapy has usually potent antitumor activity against human ovarian and prostate tumor in mice [54].

A series of β-lapachone and related naphthoquinones of natural and synthetic origin are being evaluated against drug-sensitive and drug-resistant cell lines and purified human DNA topoisomerases [55-57]. For example, a regio- and stereospecific synthesis of monoarylimino *o*-quinones derived from β-lapachone was achieved. Preliminary *in vivo* testing in assays against a standard panel of human tumor cell lines showed that several of these compounds had good scores with net cell kills [58].

The ability of other naturally-occurring naphthoquinone derivatives as antitumor agents is well documented. Naphthoquinones bearing at least one phenolic hydroxyl group, such as alkannin, Fig. **(8)** and shikonin, Fig **(9)**, are potent inhibitors of topoisomerase I [59,60]. Other investigations reported the ability of juglone, Fig. **(10)** and plumbagin, Fig. **(11)** to protect animals against chemically-induced neoplasia, such as a solid tumor (sarcoma-180) and Ehrlich ascites model [61,62].

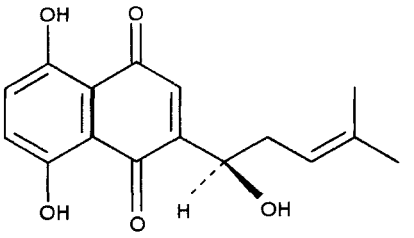

Fig. (8). Structure of alkannin

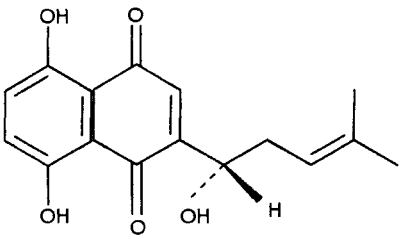

Fig. (9). Structure of shikonin

Other natural naphthoquinones, such as menadione, 1,4-naphthoquinone, 3-methyl-1,4-naphthoquinone and 2,3-dimethoxy-1,4-naphthoquinone presented antitumoral activity against the human colon carcinoma cell lines Caco-2 and HT-29 [63] and in human hepatoma cell lines [64]. More recently, Huang *et al.* [65] studied the effects of 2-mercaptophenyl-1,4-naphthoquinone, menadione and 1,4-naphthoquinone on cell proliferation and ionic currents in pituitary GH(3) lactotrophs. These studies suggest that the blockade of these ionic channels by these compounds may partly explain their inhibitory effect on the proliferation of GH(3) cells.

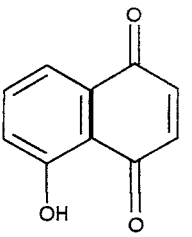

Fig. (10). Structure of juglone

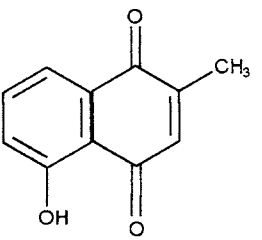

Fig. (11). Structure of plumbagin

In the search for new antitumor quinones, a series of naphthoquinone derivatives were synthesized and studies on their cytotoxicities and structure-activity relationships are being conducted. The inhibition of DNA topoisomerase I and the cytotoxic activity against L1210 cells of naphthoquinones showed the same order: 5,8-dimethoxy-1,4-naphthoquinone (DMNQ) > 6-(1-hydroxyethyl)-DMNQ > 2-(1-hydroxyethyl)-DMNQ. The steric hindrance of the substituents must be the main reason the bioactivities are lower [66]. 6-(1-azidoalkyl)-DMNQ derivatives compared with 2-(1-azidoalkyl)-DMNQ isomers exhibited higher cytotoxic activity against L1210 mouse leukaemia cells and stronger inhibition of DNA topoisomerase I, confirming involvement of steric hindrance [67]. Several DMNQ derivatives which bear an unsaturated alkyl side chain with an ester bond were synthesized and tested for cytotoxic activity on L1210 cells. The introduction of the alkenoyl moities resulted in the enhancement of their cytotoxicities [68,69]. In the same way, a series of 6-(1-acyloxyalkyl)-DMNQ derivatives were synthesized and examined for their inhibitory effect on DNA topoisomerase I and their antiproliferative activity against L1210 cells. It was found that acylation of 6-(1-hydroxyalkyl)-DMNQ derivatives

possessing alkyl chains of C-2 and C-5 enhanced both bioactivities, suggesting that an increase of electrophilicity in the quinoid moiety makes the electrophilic acylation of bionucleophiles more favorable [70]. In addition, natural products of the naphthoquinone spiroketal structural type served as lead structures for the development of novel inhibitors of two breast cancer cell lines [71].

Gokhale *et al.* [72] have synthesized a series of hydroxynaphthoquinone metal complexes as antitumor agents. The cytotoxic studies against the human breast cancer cell line MCF-7 revealed enhanced activities for the metal complexes. The highest activity is observed for the copper compound of lawsone, Fig. **(12)** (2-hydroxy-1,4-naphthoquinone).

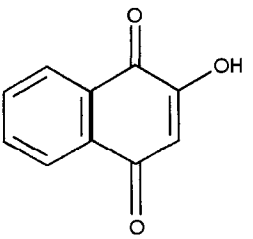

Fig. (12). Structure of lawsone

Additionally, several furanonaphthoquinones have shown useful activity in a yeat assay for DNA damaging agents and cytotoxicity in mammalian cell culture assays. These results, together with the planar aromatic character of the furanonaphthoquinone suggest that they may be acting as DNA intercalators [73,74]. In the same way, furanonaphthoquinones and analogues isolated from *Avicennia* plants having an alcoholic group in the dihydrofuran ring displayed the most potent antiproliferative activity and might be valuable as potent cancer chemopreventive agents [75]. In an attempt to improve this activity, various analogues containing a hydroxyamine chain have been synthesized [76].

Hypericin, Fig. **(13)** is a polycyclic quinone obtained from plants of *Hypericum* genus, which exhibits strong photodynamic antitumor effects.

Recent studies have demonstrated that this naphtodianthrone is a photosensitizing pigment that displays cytotoxic effects in neoplastic cell lines and that it is a powerful sensitizer for photodynamic therapy [77-81]. Photodynamic therapy has been described as a promising new modality for the treatment of cancer. Recently, Agostinis *et al.* [82] reviewed the current knowledge on the signalling pathways underlying the photocytotoxic action of hypericin. The mechanism of tumor eradication and mode of cell death induced by *in vivo* photodynamic therapy with hypericin involves vascular damage and apoptosis in the RIF-1 mouse tumor model [83].

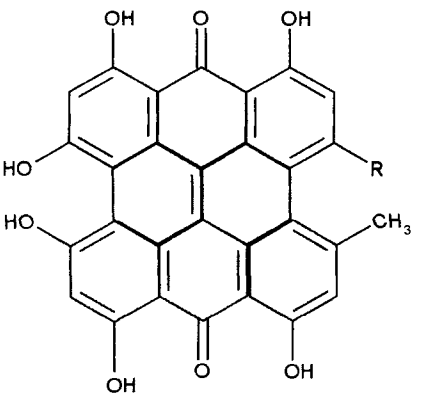

Fig. (13). Structure of hypericin

Finally, quinones from the benzoquinone group have also been reported to be antitumor agents against several tumoral cell lines, such as prostatic cancer [84] and human leukaemia K 562 cells [85].

MUTAGENIC ACTIVITY

As we have seen in the last paragraph, various tests revealed that some quinones can have an antimutagenic effect, and thus that they could have some potential as anticancer agents. However, chronic abuse of anthranoid laxatives has recently been associated with an increased risk of colorectal

carcinoma. *In vitro* and animal studies have shown a potential role of anthranoid laxatives in both the initiation and promotion of tumorigenesis. Studies in humans have also suggested tumor-promoting activities for these laxatives [86,87]. This risk is particularly important in view of the wide abuse of self-administered laxatives for chronic constipation. There are data on the genotoxic potential of anthranoids and there is evidence of a tumorigenic potential in mice and rats. For example, anthraquinone glycosides of senna and cascara were investigated for their ability to induce aberrant crypt foci in the rat colon mucosa, which are considered to be putative preneoplastic lesions. These findings suggest that senna and cascara glycosides may behave as weak promoters in rat colon carcinogenesis [88]. Similarly, toxicological studies indicated that two hydroxyanthraquinones, aloe-emodin, Fig. **(2)** and emodin, Fig. **(4)**, present as minor components in senna, may represent a genotoxic or cancerogenetic risk for man [89].

Mueller *et al.* [90] investigated the genotoxicity of 1,8-dihydroxyanthraquinones present in Chinese herbs in the comet assay, the micronucleus test and the mutation assay in lymphoma L5178Y. Emodin, Fig. **(4)** was genotoxic whereas chrysophanol, Fig. **(3)** and physcion, Fig. **(6)** showed no effects. Previously, Mueller *et al.* [91] had reported that plant-derived 1,8-dihydroxyanthraquinone derivatives emodin and danthron were clearly genotoxic in mouse lymphoma L5178Y cells, whereas chrysophanol was only weakly genotoxic and physcion not at all. Furthermore, these studies had found that these compounds bound non-covalently to DNA and inhibited topoisomerase II activity. These data support the understanding that the genotoxicity of anthraquinones is, at least in part, mediated by non-covalent DNA-binding. Other investigations support the idea that inhibition of the catalytic activity of topoisomerase II contributes to anthraquinone-induced genotoxicity and mutagenicity [92,93]. There are studies to elucidate the enzymes involved in the biotransformation of naturally-occurring 1,8-dihydroxyanthraquinones and to investigate whether biotransformation may represent a bioactivation pathway. These data indicate that the cytochrome P450-dependent biotransformation of emodin and chrysophanol may represent bioactivation pathways for these compounds [94-96].

Additionally, 1-hydroxyanthraquinones present in certain medicinal plants such as *Rubia tinctorum* L. (madder root) are genotoxic agents and mice

colon carcinogens [97]. For example, lucidin, Fig. **(14)** (1,3-dihydroxy-2-hydroxymethyl-9,10-anthracenedione) and lucidin primeveroside were shown to be responsible for the potential genotoxic activity of madder root extracts. It suggested that the presence of two hydroxy groups in the 1,3 positions is a structural requirement for the genotoxicity of hydroxyanthraquinones such as lucidin [98,99]. Other investigations showed the ability of anthraquinones in promoting other neoplastic lesions such as skin tumor and cutaneous melanoma in mice [100,101] and on the bone marrow cells of mice [102]. Several benzo- and naphthoquinones have also been shown to be oxidative mutagens [103]. More recently, Guerra *et al.* [104] have investigated the teratogenic potential of lapachol, a naphthoquinone with therapeutic potential. Results have shown a strong abortifacient effect of lapachol in rats.

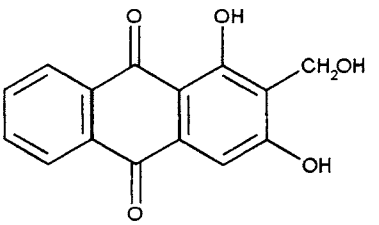

Fig. (14). Structure of lucidin

ANTI-INFLAMMATORY ACTIVITY

Polyphenols, such as quinones, are major components of many traditional herbal remedies which exhibit several beneficial effects, including anti-inflammation. For example, Cuellar *et al.* [105] investigated the topical anti-inflammatory activity of extracts from *Cassia angustifolia* Vahl. and *Rheum palmatum*, medicinal plants commonly known for their anthraquinonic content, and used in traditional East Asian medicine against different skin disorders. All the extracts significantly inhibited the edema induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in both single or multiple applications.

Several studies were designed to elucidate anti-inflammatory action mechanisms of naturally-occurring anthraquinones. Wei *et al.* [106] investigated the *in vitro* anti-inflammatory activity of the isolated anthraquinone frangulin B, Fig. **(15)** from *Rhamnus formosana* Matsum, by determining their inhibitory effects on the chemical mediators released from mast cells, neutrophils, macrophages and microgial cells. This compound showed potent inhibitory effects on tumor necrosis factor-α (TNF-α) formation in lipopolysaccharide (LPS)/interferon-γ-stimulated murine microgial cell lines N9. In the same way, Kuo *et al.* [107] studied four anthraquinones isolated from *Polygonum hypoleucum* on primary human T lymphocytes. Emodin, Fig. **(4)** had the highest suppressing activity on cell proliferation, inflammatory cytokine production and calcium mobilization. These studies suggest that the inhibitory mechanisms of emodin on activated T cell proliferation are related to the impairment of cytokine production, interleukin-2 mRNA level and calcium in the cells.

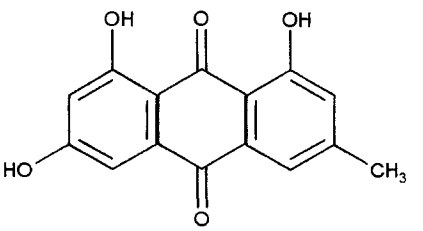

Fig. (15). Structure of frangulin

Interleukin-1β is a cytokine which plays a fundamental role in osteoarthritis pathophysiology and cartilage destruction. Targeting the activation mechanism on this cytokine appears to be important as a therapeutic approach. As the interleukin-1 converting enzyme is the physiological modulator of the production of active interleukin-1β, several studies have investigated the effect of two anthraquinones used in the treatment of osteoarthritic patients, diacerhein and its active metabolite rhein, Fig. **(5)**, on interleukin-1 expression and synthesis in human osteoarthritic cartilage. These results provide novel regulatory mechanisms by which

diacerhein and rhein could exert the effect on interleukin-1 in osteoarthritic cartilage [108,109]. Previously, Carney *et al.* [110,111] examined the effects of diacetylrhein and several related anthraquinone analogues on the synthesis, turnover and composition of cartilage in an *in vivo* experimental model of osteoarthritis. Diacetylrhein was well tolerated by the experimental animals, but did not produce significant changes in the synthesis or turnover of proteoglycans.

Pelletier *et al.* [112] evaluated the *in vitro* effects of diacerhein and its active metabolite rhein, Fig. **(5)**, on the production of nitric oxide (NO), prostaglandins (PGs), cyclooxygenase-2 (COX-2), as well as the production and expression of the inducible nitric oxide synthase (iNOS) in human osteoarthritic chondrocytes. Diacerhein and rhein are potent inhibitors of interleukin-1β induced NO production by chondrocytes and cartilage, without reducing PGE_2 production. Chen *et al.* [113] investigated the effect of other naturally-occurring anthraquinones on LPS-induced NO production and i-NOS and COX-2 gene expression in RAW2647 macrophages. The results indicate that only emodin concentration dependently inhibited LPS-induced NO production. On the other hand, Jun N-terminal kinase (JNK) is a stress-activated protein kinase that can be induced by inflammatory cytokines, bacterial endotoxins, osmotic shock, UV radiation and hypoxia. Several studies support targeting JNK as an important strategy in inflammatory disease. Bennett *et al.* [114] reported the identification of an anthrapyrazolone series with significant inhibition of JNK. These compounds inhibited the phosphorylation of JNK, the expression of inflammatory genes COX-2, interleukin-2, interpheron-γ, TNF-α, and prevented the activation and differentiation of primary human CD4 cell cultures.

Several observations suggest that naphthoquinones may also have effects on the production of inflammatory mediators, including cytokines. Fibroblasts are recognized as a rich source of cytokines, and Reddi *et al.* [115] have examined the effect of various natural naphthoquinones on the production of interleukin-6 by LPS-stimulated human gingival fibroblasts. Naphthoquinone vitamins, e.g. vitamin K, Fig. **(16)**, are widely recognized for their role in the γ-carboxylation of specific glutamyl residues in coagulation, anti-coagulation and extra-hepatic proteins. However, there have been reports that these compounds can exert actions other than those

normally associated with protein γ-carboxylation. These compounds are capable of inhibiting interleukin-6 production probably by a mechanism related to the redox capacity of these naphthoquinones. Other naturally-occurring quinones also have effects on the production of other inflammatory mediators such as protein kinase C [116,117], leukotriene B_4 (lipoxygenase activity) [118-120] and on phospholipase A_2 activity [121].

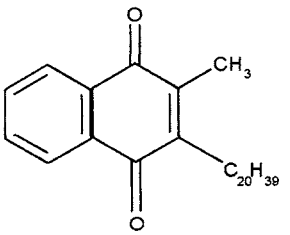

Fig. (16). Structure of vitamin K

A series of 2-substituted 3-chloro-1,4-naphthoquinones were synthesized and their anti-inflammatory activities were evaluated. The structure-activity relationships in this series were also examined. Most of the 2-alkyl/arylcarboxamido derivatives of 3-chloro-1,4-naphthoquinones showed potent activity [122,123]. Selected naphthoquinone compounds were investigated for 5-lipoxygenase inhibiting and antioxidative properties. There is a clear-cut correlation of both qualities in those compounds with a 3-hydroxy function and with two, one or without any tert-butyl group at the phenyl moiety [124].

ANTIOXIDANT ACTIVITY

The antioxidant properties of naturally occurring anthraquinones and anthrones were evaluated using different model systems. For example, the antioxidant activity of these compounds was studied on the inhibition of peroxidation of linoleic acid. These results suggest that the antioxidant mechanism for two anthraquinones, emodin, Fig. **(4)** and aloe-emodin, Fig. **(2)**, possibly depends on scavenging hydroxy radicals, while the pro-oxidant

activity exhibited by chrysophanol, Fig. **(3)** might be due to the enhanced production of free radicals [125,126]. Several investigations reported the antioxidant actions of anthraquinone compounds found in *Rheum* and *Cassia* by measuring inhibition of pyrogallol autoxidation and radical scavenger activity against hydroxy radicals generated via Fenton reactions. Emodin was shown to be a potent inhibitor of superoxide radicals in contrast to other compounds [127,128].

More recently, Choi *et al.* [129] investigated the antioxidant activities of alaternin, Fig. **(17)** (2-hydroxyemodin) and emodin, Fig. **(4)** for their respective potential to inhibit lipid peroxidation in the linoleic acid system, to inhibit total reactive oxygen species generation in kidney homogenates, to inhibit peroxynitrite formation and to scavenge authentic peroxynitritres. These results indicate that alaternin is a potentially effective and versatile antioxidant and can be used to protect biological systems and functions against various oxidative stresses. Sheu and Chiang [130] investigated eighteen natural anthraquinones and related compounds for their inhibitory effects on xanthine oxidase. This enzyme catalyses the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. The results showed that anthrarobin and purpurin had moderate effects on xanthine oxidase inhibition, and both of them induced mixed type (competitive, non-competitive) inhibition with respect to the substrate xanthine.

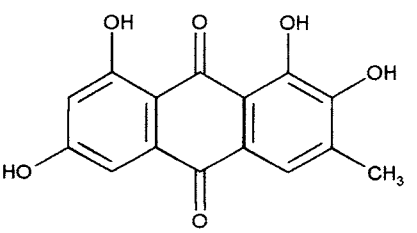

Fig. (17). Structure of alaternin

Antioxidant activity of other natural quinones, such as ubiquinone, phylloquinone and menadione was studied in the model system of the methyl oleate-initiated oxidation. The menadione antioxidant activity was shown to

be two-fold higher as compared with the inhibitory activity of other natural quinones [131]. In the reduced form, ubiquinone functions as a lipid-soluble antioxidant and protects cells from lipid peroxidation [132].

Kumbhar *et al.* [133] also investigated the modulation of radiation-induced lipid peroxidation in synaptosomes by iron (II) and iron (III) complexes of two naturally occurring and therapeutically relevant naphthoquinones: juglone, Fig. **(10)** and lawsone, Fig. **(12)**. At lower concentrations the complexes enhance lipid peroxidation, predominantly through redox cycling as observed for iron (II)-juglonate, while at higher concentrations the complexes tend to limit lipid peroxidation through fast recombination. The antioxidant properties of 2,3,5,7,8-pentahydroxy-1,4-naphthoquinone (echinochrome A) were linked with the scavenging of peroxy radicals in liposomes, trapping of superoxide anion radicals, and binding of ferrous ions to inactive complexes [134]. Other natural naphthoquinones, such as shikonin, Fig. **(9)**, show highly efficient antioxidative activities against several types of reactive oxygen species: singlet oxygen, superoxide anion radical, hydroxy radical and tert-butyl peroxyl radical, as well as iron-dependent microsomal lipid peroxidation. Based of the scavenging abilities of shikonin, the compound was concluded to react directly with reactive oxygen species and exhibits antioxidative activity which in turn exerts anti-inflammatory activity [135].

Several studies were also designed to evaluate the antioxidant properties of St. John's Wort (*Hypericum perforatum* L.), an herbal drug used in the treatment of burns, bruises, swelling and anxiety. Commercially available formulations of St. John's Wort, standardized to the naphthoquinone hypericin, Fig. **(13)**, inhibit free radical production in both cell-free and human vascular tissue [136].

Several quinonic compounds have been synthesized and their antioxidant activities are being evaluated. For example, a series of arylthiolated-2,3-dimethoxy-1,4-benzoquinones were chemically prepared and tested for their effect on the respiratory system and the lipid peroxidation in bovine heart mitochondria. These quinones were as efficient as exogenous ubiquinone for the inhibition of lipid peroxidation. 5- and 5,6-diarylthio groups on the quinone ring were found to be favorable for the inhibition of the respiratory system and lipid peroxidation [137]. Giorgini *et al.* [138] studied the

reactivity of several quinones and of the corresponding quinols toward carbon- and oxygen-centered radicals. All quinones bearing at least one nuclear position free readily react with alkyl and phenyl radicals to afford the alkylated quinones.

ANTIPSORIATIC ACTIVITY

Some naturally occurring quinonic compounds appear to be promising as effective antipsoriatic agents, due to their potent activity against the growth of human keratinocytes. Antipsoriatic anthrones are among the most commonly used topical agents for the treatment of psoriasis. These drugs generate reactive oxygen species during their auto-oxidation under physiological conditions. Several studies have indicated that activation of molecular oxygen by anthrones may play a critical role in their mechanism of action at the molecular level. This mechanism is related to their redox activity leading to the production of active oxygen species which include singlet oxygen, superoxide anion radical and hydroxy radical [139,140]. In 1996, Muller [141] summarized the evidence pointing toward the significance of oxygen activation and radical formation in antipsoriatic action and induction of skin inflammation of anthrones.

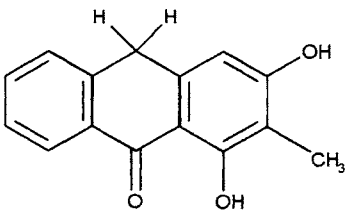

Fig. (18). Structure of anthralin

Anthralin, Fig. **(18)** is the most common therapeutic agent among a small number of pro-oxidant 9-anthrones, effective in the topical treatment of psoriasis. However, the usefulness of this drug is diminished by toxic side effects, including skin irritation and inflammation. Several studies suggest

that oxidative stress generated at the site of anthralin treatment alters the expression of dermal chemokines and other cytokines, resulting in the recruitment of inflammatory cells. Systemic antioxidant administration may provide opportunities for therapeutic intervention against anthralin-associated toxicities [142].

Heterocyclic substituted derivatives of the antipsoriatic anthralin were synthesized and evaluated *in vitro* for their antiproliferative action against keratinocytes and their ability to induce keratinocyte differentiation. The indole-2-carboxylic acid analogues exhibited the same excellent antiproliferative activity as anthralin and also induced terminal differentiation of keratinocytes. As a benefit of their strongly diminished potential to generate oxygen radicals, these synthetic compounds did not induce damage of keratinocyte membranes [143]. 10-arylthio derivatives of anthralin are also of interest in the search for new antipsoriatic agents. These synthetic compounds have been evaluated for their ability to inhibit the growth of the human keratinocyte cell line HaCaT. Biological tests have shown that 10-benzylthio-1,8-dihydroxy-9(10H)-anthracenone slightly inhibited the HaCaT cells [144,145]. Muller *et al.* [146] described the synthesis and structure-activity relationships of a series of novel 10-arylacetyl-1,8-dihydroxy-9(10H)-anthracenones. Several compounds were identified which are equally potent as inhibitors of human keratinocyte growth as the antipsoriatic agent anthralin. Additionally, Muller *et al.* [119] synthesized 10-phenylbutyryl-substituted anthracenones as inibitors of keratinocyte growth.

In the naphthoquinone group, a number of lapacho compounds, the most common naphthoquinonic constituents of the inner bark of *Tabebuia impetiginosa* (Mart. ex D. C.) Standl were evaluated *in vitro* against the growth of the human keratinocyte cell line HaCaT. All compounds inhibited keratinocyte growth and appear to be promising as effective antipsoriatic agent [147].

ANTIVIRAL ACTIVITY

The development of new antiviral drugs, specially herbal preparations, remains desirable. Several studies screened natural quinones and plant extracts containing these compounds for inhibitory activity against several

DNA and RNA viruses. For example, 152 methanol and water extracts of different parts of 71 plants commonly used in Sudanese traditional medicine were screened for their inhibitory effects on hepatitis C virus protease using *in vitro* assay methods. Thirty-four extracts showed significant inhibitory activity. From the *Embelia schimperi* D. C. extract, two benzoquinones, embelin and 5-O-methylembelin, were isolated and found to be potent inhibitors [148,149].

Hypericin, Fig. **(13)**, a natural naphthoquinone of the common St. John's Wort plant *Hypericum perforatum* has *in vitro* activity against several viruses, including bovine diarrhoea virus, a pestivirus with structural similarities to the hepatitis virus [150]. Several investigations suggest that some plants of the genus *Hypericum* from Southern Brazil, such as *Hypericum connatum* Lam, *Hypericum caprifolium* Boiss and *Hypericum polyanthemum* Klotzsch ex Reichardt also contain compounds with potential antiviral activity against lentivirus [151].

Quinones with one, two and three aromatic rings are a new class of inhibitors of human immunodeficiency virus-1 (HIV-1) proteinase, an enzyme essential for replication of HIV and an important drug target in the treatment of acquired immunodeficiency syndrome (AIDS). For example, the trimeric quinone framework of conocurvone is crucial for the potent anti-HIV activity of this compound [152,153]. Recently, Emadi *et al.* [154] described a new synthesis of these trimeric quinones. Substituted anthraquinones bearing hydroxyl substituents as one of their three rings were the most potent of these inhibitors. In an effort to develop new drugs preventing the growth of HIV, Min *et al.* [155] developed an *in vitro* assay method of ribonuclease H (RNase H) activity associated with reverse transcriptase (RT) from HIV-1. Some naphthoquinones, such as 1,4-naphthoquinone, vitamin K, Fig. **(16)**, juglone, Fig. **(10)** and plumbagin, Fig. **(11)** moderately inhibited RNase H activity and others, including naphthazarin, Fig. **(19)** and shikonin, Fig. **(9)** showed weak inhibition. Diterpenoid quinones such as tanshinones and aryl-substituted naphtho- and anthraquinones also had moderate inibition against RNase H activity [156].

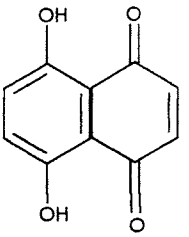

Fig. (19). Structure of naphtharazin

In a screening study with plant extracts, a rhubarb root extract with 4-6% hydroxyanthracene derivatives showed a promising activity for topical treatment of herpes labialis [157]. 31 herbs used in Chinese medicine were also screened to develop anti-herpes simplex virus type I (HSV-1) compounds from plants. These results showed that ethanolic extract of *Rheum officinale* prevented the process of virus attachment and penetration, and has a potential value as source of new powerful anti-HSV compounds [158]. The proteases encoded by the herpes virus, including HSV-1 and human cytomegalovirus (HCMV) are attractive targets for antiviral drug development because of their important roles in viral replication. 1,4-dihydronaphthalene and naturally-occurring naphthoquinones and anthraquinones were found to be potent inhibitors of HSV-1 protease [159-161]. Additionally, a random screening approach has identified 2-chloro-3-substituted-1,4-naphthoquinones as potent inactivators of HCMV protease [162].

Natural quinones also exert antiviral activity against other viruses, such as the Epstein-Barr virus and poliovirus type 2 and 3 [163-165]. For example, chrysophanic acid (1,8-dihydroxy-3-methylanthraquinone) isolated from the Australian Aboriginal medicinal plant *Dianella longifolia* Street has been found to inhibit the replication of poliovirus type 2 and 3 *in vitro*. Four structurally-related anthraquinones (rhein, Fig. **(5)**, 1,8-dihydroxyanthraquinone, emodin, Fig. **(4)** and aloe-emodin, Fig. **(2)**) were also tested for activity against poliovirus type 3, although none of them was as active as chrysophanic acid against the virus [166].

ANTIFUNGAL ACTIVITY

In natural products, this activity is usually associated with the presence of phenolic functions. Investigations have been conducted to study the mechanism of action of antifungal quinones, particularly naphthoquinones, towards several fungi such as *Candida albicans* [167,168] and *Fusarium* spp. [169]. The growth of the white-rot basidiomycete *Pleurotus sajor-caju* in malt-agar plates was also inhibited by three naturally-occurring plant-derived naphthoquinones: juglone, Fig. **(10)**, lawsone, Fig. **(12)** and plumbagin, Fig. **(11)** [170].

Mahoney *et al.* [171] investigated the effect of a series of naphthoquinones (1,4-naphthoquinone, juglone, Fig. **(10)**, 2-methyl-1,4-naphthoquinone and plumbagin, Fig. **(11)**) on fungal viability and aflatoxigenesis. Aflatoxins are metabolites produced on infection with *Aspergillus flavus*. The naphthoquinones delayed germination of the fungus and were capable of completely inhibiting growth at higher concentrations. Structural features associated with decreased fungal viability and the greatest effect on aflatoxigenesis are the presence of a 5-hydroxyl or 2-methyl substituent, but there is no significant additive effect when both of these substituents are present. Lee *et al.* [172] investigated the effects of naturally-occurring compounds from plants on biotransformation of aflatoxin B-1. These results demontrate that some anthraquinones may have significant inhibitory effects on the metabolic transformation of aflatoxins to their hepatotoxic or carcinogenic derivatives or, alternatively, may promote their transformation into nontoxic products.

In the anthraquinone group, rhein, Fig. **(5)**, physcion, Fig. **(6)**, aloe-emodin, Fig. **(2)** and chrysophanol, Fig. **(3)** isolated from *Rheum emodi* L. rhizomes exhibited antifungal activity against *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton mentagrophytes* and *Aspergillus fumigatus* [173]. Different extracts containing anthraquinones of both fresh and dry leaves of *Aloe eru* Berger, *Aloe vera* and *Aloe arborescens* were also screened for their antifungal activity against *Aspergillus niger*, *Cladosporium herbarum* and *Fusarium moniliforme* [174].

ANTIBACTERIAL ACTIVITY

Several investigations have reported the study of the activity of quinone derivatives and plant extracts containing these compounds against several pathogenic bacteria. *In vitro* antibacterial testing was carried out using the disk diffusion method against Gram-positive *Staphylococcus aureus*, *Staphylococcus epidermis* and Gram-negative *Pseudomonas aeruginosae*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Escherichia coli*. Ethanol extracts of *Cassia occidentalis* L. and *Cassia alata* L. and metabolite-rich fractions (anthraquinones and sennosides, Fig. **(1)**) of leaves, pods, flowers and callus have been tested against indicator human pathogenic bacteria. The anthraquinones were found to be more active against *Escherichia coli* and *Staphylococcus aureus*, while sennosides were most active against *Aspergillus flavus* [175,176].

Hatano *et al.* [177] also studied the effect of anthraquinone derivatives isolated from *Cassia tora* L. on *Escherichia coli* K12, *Pseudomonas aeruginosae* and some strains of *Staphylococcus aureus*. Among them, torachrysone, toralactone, aloe-emodin, Fig. **(2)**, rhein, Fig. **(5)** and emodin, Fig. **(4)** showed noticeable antibacterial effects. Some quinoid compounds such as aloe-emodin and thymoquinone showed potent antibacterial activity against methicillin-resistant *Staphylococcus aureus*. Aloe-emodin was basteriostatic while thymoquinone was bactericidal. The structure-function relationship study suggests that hydrophilic groups at position 3 of anthraquinone and methyl groups of benzoquinones are very important for their activity [178]. More recently, Manojlovic *et al.* [179] investigated the antimicrobial activity of an extract and isolated anthraquinones from *Caloplaca schaereri* (Flöcke) Zahlbr.

In the naphthoquinone group, two dimeric naphthoquinones, diospyrin and isodiospyrin isolated from the root of *Diospyros piscatonia* (Gurke) and *Euclea natalensis* D. C., common ingredients in several folk medicines, have been shown to have a broad spectrum of antibacterial activity, e.g., against *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Salmonella choleraesuis* serotype *typhi*, *Mycobacterium chelonae* and *Mycobacterium tuberculosis* [180,181]. Yang *et al.* [182] isolated a single bioactive compound, 2-methoxy-1,4-naphthoquinone, from the ethanol extract of the dried aerial

parts of *Impatients balsamita* L. Its antomicrobial activity was evaluated using 12 bacterial strains. Five Gram-positive and two Gram-negative bacteria were highly sensitive to this compound. Mehrabian *et al.* [183] detected the antimicrobial effects of an extract containing naphthoquinonic compounds from *Rubia tinctorum* and *Juglans regia* L. on some bacteria such as *Bacillus subtilis*, *Bacillus cereus* and *Bacillus mycoides*. The antimicrobial effects are microbicidal. Ethanolic extracts of 20 selected plants species used by Yemeni traditional healers to treat infectious diseases were also screened for their antibacterial activity against both Gram-positive and Gram-negative bacteria. The ethyl acetate extract of *Lawsonia inermis* L., known to contain naphthoquinonic compounds, was found to be the most active against all bacteria in the test system [184].

Rothery *et al.* [185] have used two hydroxylated naphthoquinol analogues, reduced plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) and reduced lapachol (2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone) as substrates from *Escherichia coli* anaerobic reductases. Additionally, the 2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine revealed good activity against *Staphylococcus aureus* [186]. Relationships between the chemical structure and antibacterial activity of these compounds was studied. Introduction of a second methyl group in C-3 of the isoxazol ring reduced the antibacterial activity, while a second aminoisoxazolyl function in C-2 of the naphthoquinone ring inhibited the biological activity [187]. Several 1,4-naphthoquinone derivatives having a hydrazino side chain were synthesized from diazo-naphthalene-1,2,4-trione and tested as potential antimicrobial agents against *Staphylococcus aureus* [188].

In the benzoquinone group, inhibition assays using *Escherichia coli* and *Saccharomyces cerevisiae* revealed the inhibitory effects of 1,4-benzoquinone and toluquinone against all tested microorganisms [189].

PROTOZOOCIDAL ACTIVITY

The protozoocidal activity of quinone derivatives was evaluated *in vitro* against *Plasmodium*, *Leishmania*, *Trypanosoma*, *Trichomonas* and *Toxoplasma*. Malaria is a major tropical diseases which kills two million people annually. The population at risk from this disease has increased

because of the difficulties in erradicating the mosquito vector in the endemic regions, and the emergence and spread of parasite resistance to all the commonly used antimalarials.

Lapachol is a naphthoquinone from *Tabebuia* spp. used as an antimalarial agent with strong activity against *Plasmodium falciparum* [190]. Four naphthoquinones from *Kigelia pinnata* D. C. rootbark were assessed *in vitro* against chloroquine-sensitive (T9-96) and-resistant (K1) *Plasmodium falciparum* strains. Isopinnatal, kigelinol and isokigelinol exhibited lower activity against both strains [191]. More recently, Kapadia *et al.* [192] have identified aminonaphthoquinones as a class of antimalarial compounds with activity against *Plasmodium falciparum*. Among these compounds, 2-amino-3-chloro-1,4-naphthoquinone is the most potent. Another medicinal plant such as the root of *Nephentes thorelii* L. yielded plumbagin, Fig. **(11)**, 2-methylnaphthazarin and droserone, Fig. **(20)**, with antimalarial potential [193]. Other antimalarial naphthoquinones such as atovaquone inhibit malarial dehydroorotate dehydrogenase by inhibiting electron transport [194]. Atovaquone is a chemotherapeutic agent used to treat pneumonia caused by *Pneumocystis carinii* in some immunocompromised patients [195].

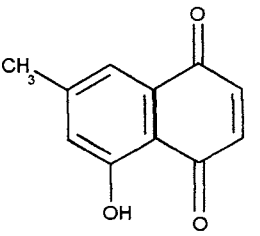

Fig. (20). Structure of droserone

A series of monomeric and dimeric naphthoquinones with potential for treatment of *Leishmania* infections were identified *in vitro* using a direct cytotoxicity assay against extracellular promastigotes of *Leishmania* spp. [196,197]. Lapachol was evaluated *in vitro* against intracellular amastigotes of *Leishmania braziliensis* and then tested in an animal model (hamster) to try to reproduce the leishmanicidal activity. *In vitro* lapachol exhibited an

anti-amastigote effect, whereas *in vivo* it did not prevent the development of *Leishmania*-induced lesions [198].

Cryptotanshinone is a quinoid diterpene with a nor-abietane skeleton isolated from roots of the Iranian medicinal plant *Perouskia abronatoides* L. which exhibited leishmanicidal activity *in vitro*. These findings provide a rationale for the traditional use of the roots in Iran as a constituent of poultices for treatment of cutaneous leishmaniasis [199]. More recently, Valderrama *et al.* [200] synthesized several eurylfurylquinones and hydroquinones from activated monosubstituted 1,4-benzoquinones and studied their *in vitro* activities against *Leishmania amazonensis*.

Additionally, several naphthoquinones showed remarkable anti-trypanosomal activity, such as four naphthoquinones isolated from *Kigelia pinnata*: 2-(1-hydroxyethyl)-naphthol[2,3-b]-furan-4,9-quinone, isopinnatal, kigelinol and isokigelinol. These compounds were assessed for anti-trypanosomal activity against *Trypanosoma brucei brucei* and *Trypanosoma brucei rhodesiense* bloodstream form trypomastigotes *in vitro* [201]. These types of naphthoquinones, isolated from *Calceolaria sessiles* D. C. were tested against *Trypanosoma cruzi* epimastigotes and they produced a temporary increase of oxygen consumption in *Trypanosoma cruzi*, suggesting the generation and participation of free radicals [202]. With the aim of understanding the influence of redox potentials on the trypanocidal activity, a series of quinones were tested *in vitro* with trypomastigotes of *Trypanosoma cruzi* [203]. Trypanothione reductase is both a valid and attractive target for the design of new trypanocidal drugs. Starting from menadione, plumbagin, Fig. **(11)** and juglone, Fig. **(10)**, three distinct series of 1,4-naphthoquinones were synthesized as potential inhibitors of trypanothione reductase from *Trypanosoma cruzi* [204-206]. Naphthol[2,3-b]-thiophen-4,9-quinone and derivatives, and pyranobenzoquinones were also chemically prepared and evaluated for their trypanocidal activity [207,208].

Naphthoquinones isolated from the wood of trees of the families Bignoniaceae and Verbenaceae have been subjected to an interdisciplinary study since the seventies, when Dr. Gilbert, at the Federal University of Rio de Janeiro, launched a program on the chemistry of natural products active against endemic diseases. Recently, De Moura *et al.* [209] have described the synthesis of five naphthoimidazoles derived from this program and their

activity towards *Trypanosoma cruzi*. The biological activities of the naphthoquinone lapachol and its cyclization product β-lapachone extracted from trees of the genus *Tabebuia*, have also been intensively studied. In studies on heterocyclic derivatives obtained from the reaction of these naphthoquinones with amino-containing reagents, 22 derivatives of β-lapachone, nor-β-lapachone and lapachol were synthesized and their activities against trypomastigote forms of *Trypanosoma cruzi* were evaluated [210]. Previously, Pinto *et al.* [211] reported the biological activity of allyl derivatives of lawsone, Fig. **(12)**, a natural naphthoquinone from *Lawsonia alba* Lam. inactive against *Trypanosoma cruzi*. The introduction of an allyl group in lawsone gives rise to O-allyl-lawsone and C-allyl-lawsone that have shown activity against the parasite. In the anthraquinone group, aloe-emodin, Fig. **(2)** was the only compound active against *Trypanosoma brucei* [212].

Finally, two 3-alkyl-substituted-2-hydroxy-1,4-naphthoquinones were evaluated for activity against *Toxoplasma gondii in vitro* and in murine models of acute toxoplasmosis. These results indicate that treatment with these compounds have promising activity [213].

MOLLUSCICIDAL ACTIVITY

Several studies have investigated the potential of natural naphthoquinones as the basis for a new class of pest control agents. For example, structure-activity studies on two pesticidal naphthoquinones from *Calceolaria andina* Benth. both containing a key structural feature not previously investigated, led to the identification of analogues with commercial levels of activity [214,215]. A series of compounds with structures based on these naphthoquinones have been synthesized. A feature of the series is the lack of resistance shown by strains resistant to established classes of pesticides. The tetra-substituted carbon atom in the side-chain is important for this activity as can be observed in natural products. Activity of the compounds examined was particularly high against *Bemisia tabaci* and *Tetranynchus urticae* in direct-contact tests, but was much lower than expected in leaf-dip test [216].

Dos Santos *et al.* [217,218] tested the activity of lapachol and other 2-hydroxy-3-alkylnaphthoquinones possessing nitrogenated alkyl chains against the snail *Biomphalaria glabrata*. Lapachol, isolapachol and nor-

lapachol showed strong molluscicidal activity against the adult snail. As the derivatives can be synthesized without any difficulty, large-scale synthesis and field tests can be conducted, with a view to large-scale molluscicidal programs. The main mode of herbicidal activity of 2-hydroxy-3-alkyl-1,4-naphthoquinones has been shown to be inhibition of photosystem II. Other modes of action were also investigated using two representative compounds of this group. They did not show any activity on photosystem I or mitochondrial complex I, or generate toxic oxygen radicals by redox cycling reactions [219].

Weissenberg *et al.* [220] investigated the effect of substituted and ring changes in naturally occurring naphthoquinones on the feeding response of the larvae of the Mexican bean beetle *Epilachna varivestis*. Among the model compounds, 2-chloro-3-amino-1,4-naphthoquinone and α-naphthylamine displayed appreciable activity. More recently, Magdum *et al.* [221] investigated the molluscicidal activity of two naturally occurring naphthoquinones, plumbagin, Fig. **(11)** from *Plumbago* spp. and juglone, Fig. **(10)** from *Juglans regia*, using the red cotton bug *Dysdercus koenigii*. Their activity was compared with synthetic naphthoquinones, two benzoquinones (2,6-dimethyl- and 2,3,6-trimethylbenzoquinone) and a hydroquinone (2,6-dimethylhydroquinone). Among the natural products, juglone induced more sterilizing effects than plumbagin. Plumbagin and azadirachtin also alter the activity profiles of two lysosomal enzymes in the fat body of *Helicoverpa armigera* [222]. Additionally, anthraquinones from *Rheum palmatum* and *Rumex dentatus* L. have shown molluscicidal activity against the schistosome vector snails *Oncomelania*, *Biomphalaria* and *Bulinus* [223].

ANTIDEPRESSANT ACTIVITY

Tricyclic antidepressants are the mainstay of treatment of painful polyneuropathy, but cannot be used in a substantial number of patients. St. John's Wort (*Hypericum perforatum*) is a herbal antidepressant which may act via mechanisms similar to tricyclics. Clinical trials have extensively reported the ability of *Hypericum perforatum* extracts to exert a significant antidepressant activity [224-226]. Hypericins, Fig. **(13)** are considered to be one of the compounds contributing to the activity of the extract [227]. These

naphthodianthrones exist in various forms in the *Hyperici* herb. Protopseudohypericin and protohypericin (protopigments) are converted into pseudohypericin and hypericin (pigments) under the action of light [228-230].

Several investigations have studied the *in vivo* antidepressant activity of this herb and of compounds isolated from it. For example, a commercially available extract of the aerial parts of *Hypericum perforatum* L1160 and hypericin, Fig. **(13)** showed pronounced activity in selected animal bioassays. These include the forced swimming test and the tail suspension test, used to determine antidepressant activity, and tests indicating activity on the central nervous system, such as body temperature and ketamine-induced sleeping time [231,232].

Hypericum perforatum is one of the leading psychotherapeutic phytomedicines, and because of this great effort has been devoted to clarifying its *in vitro* mechanism of action. *Hypericum* is a nonspecific inhibitor of the neuronal uptake of monoamines: serotonin (5-HT), noradrenaline (NA), dopamine (DA) as well as ν-aminobutyric acid (GABA) and glutamate [233,234]. Cott [235] and Raffa [236] investigated a crude *Hypericum* extract and a sample of pure hypericin in a battery of *in vitro* receptor assays, and two enzyme assays. Hypericin had affinity only for NMDA receptors while the crude extract had significant receptor affinity for adenosine (nonspecific), GABA A and B, benzodiazepine, inositol triphosphate and monoaminooxidase A and B. Several studies have investigated the possible involvement of receptors and of serotonergic mechanisms in the effects of *Hypericum perforatum* extract containing 0.3% hypericin, on immobility time in the forced swimming test. These results suggest that the antidepressant-like effect of *Hyperici* herb in the forced swimming test may be mediated by interaction with receptors and to some extent by increased serotonergic neurotransmission [237-240]. Simmen *et al.* [241] studied the effect of extracts and some constituents of St. John's Wort at various central nervous system receptors. Binding inhibition was examined for the G-protein coupled opiod, 5-HT, histamine, neurokinin and corticotropin releasing factor receptors, for the steroid strogen-receptor and for the ligand-gated ionchannel GABA A receptor. Hypericin showed the most potent binding inhibition of all tested constituents.

More recently, Butterweck *et al.* [242] have investigated the chronic effects of St. John's Wort and hypericin on regional brain amine metabolism. These data clearly show that long-term, but not short-term, administration of St. John's Wort and its active constituent hypericin modify levels of neurotransmitters in brain regions involved in the pathophysiology of depression. Previously, Butterweck *et al.* [243] used in situ hybridization histochemistry to examine in rats the effects of short-term (two weeks) and long-term (eight weeks) administration of *Hypericum* extract and hypericin on the expression of genes that may be involved in the regulation of the hypothalamic-pituitary-adrenal axis. Select stress-induced changes in gene transcription in particular brain areas can be prevented by long-term treatment with the herbiceutical St. John's Wort.

Recent pharmacologic evidence suggests that other constituents of this plant, apart from hypericins, may be of greater importance in the reported psychotherapeutic activity. Phenylpropanes, flavonol derivatives, biflavones, proanthocyanidins, xanthones, phloroglucinols, some aminoacids, naphthodianthrones and essential oil constituents are the natural plant products known from the crude drug of *Hypericum perforatum*. These compounds are discussed with respect to their possible contribution to the clinically-demonstrated antidepressant efficacy of extracts obtained from the *Hyperici* herb [244-254].

Despite the wide use of St. John's Wort as an antidepressant, recent investigations have reported a probable drug interaction between this herb and/or hypericin and several drugs [255-258]. Recent clinical studies have demonstrated that *Hypericum* extracts increase the metabolism of various drugs, including combined oral contraceptives, cyclosporin, indinavir and digoxin. St. John's Wort was reported to substantially decrease blood/plasma concentrations and the efficacy of these drugs. These results indicate a direct inducing effect of St.John's Wort on intestinal P-glycoprotein/MDR1 (in rats and humans), hepatic cytochrome P450 3A2 (in rats), and intestinal and hepatic cytochrome P450 3A4 (in humans) [259-261]. Several studies have been conducted into the potential of its interaction with other drugs due to the induction of cytochrome P450 isoenzymes 1A2 and and 3A4 by the component hypericin. *In vitro* assays indicate that hypericin is a potent antagonist of cleavage complex stabilization by the chemotherapeutics

etoposide and amsacrine. This antagonism appears to be due to the ability of hypericin to intercalate or distort DNA structure, thereby precluding topo II binding and/or DNA cleavage [262].

OTHER ACTIVITIES AND USES

As we can see in the present review, plant quinones are of interest in many respects. Preparations and products derived from natural quinones, and their synthetic relatives, serve medicinal, therapeutical and technological purposes. In technology, the range of interest extends from timber and dye material to semiconductors. Among the possible new materials for microelectronics, quinones have a number of significant advantages. Similarly, polymers with quinone functionality possess biodegradability and are promising candidates for functional materials in the future. In the search for the polymers of natural products, a natural quinone extracted from *Embelier libes* D. C., embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), were electrochemically polymerized and their properties investigated [263,264].

The usefulness of the intensively-coloured naturally-occurring quinones as dyes (e.g., madder, kermes or cochineal) was recognised early in civilisation. Common madder (*Rubia tinctorum*) produces anthraquinone pigments in its roots, one of them being alizarin, Fig. **(21)** (1,2-dihydroxy-anthraquinone) which has been used for dyeing textiles since ancient times, and has an important industrial value [265]. The leaves of *Lawsonia inermis* (popularly named as henna) have also been used since ancient times for decorating and dyeing hands, soles, beard and hair and to impart beautiful shades of a dark red color. The naphthoquinone lawsone, Fig. **(12)**, a brown powder, was isolated from the leaves of henna and was used as a staining agent [266].

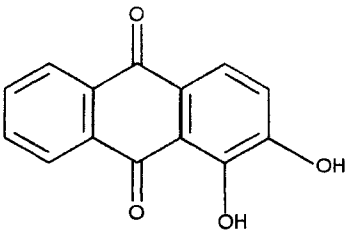

Fig. (21). Structure of alizarin

Carmine, Fig. **(22)** (E120) is a natural red dye of anthraquinonic type extracted from the dried females of the insect *Dactylopins coccus* var. *costa* (cochineal), which are widely used as additives in various foods. However, the risk of sensitization to reactive dyes is well established [267]. Carmine has been reported to cause hypersensitivity reactions and has been implicated as an ethiologic agent of occupational asthma, but the allergens involved have not yet been identified [268-271]. Several investigations have reported numerous cases of anaphylactic reaction to carmine [272-275]. Immunoglobulin E-hypersensitivity is a suggested mechanism to explain adverse reactions from carmine-containing products [276,277].

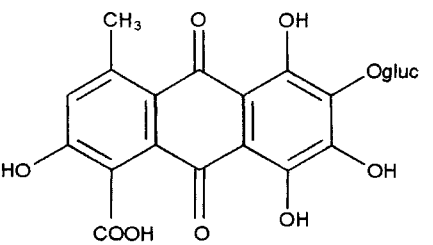

Fig. (22). Structure of carmine

Various quinones in the sawdust of commercial timbers are also capable of inducing allergic contact dermatitis and allergic bronchial asthma in

people operating in woodworking industries [278-281]. Similarly, several cases of hairdressers who develop an immediate-type hypersensitivity with urticaria, rhinitis and bronchial asthma on exposure to henna have also been reported [282-284]. Finally, in medicine, pharmacy and technology, the range of interest of naturally-occurring quinones covers their therapeutical as well as their allergological and toxicological properties [285-287].

Other pharmacological properties reported from natural and synthetic quinones, which range from chemically complex phytotherapeutics to simple pure drugs are listed below. For example, Satoh *et al.* [288] studied the effects of 17 kinds of Kampo-formulations and the constitutive crude drugs prescribed for the treatment of peptic ulcer, on H-K-ATPase activity. Among them, the *Rhei* rhizome had a notable inhibitory effect. H-K-ATPase activity was inhibited by sennoside A and B, Fig. (**1**), two anthraquinonic constituents of this herb. Four compounds of an anthraquinonic type isolated from this medicinal plant (emodin, Fig. (**4**), rhein, Fig. (**5**), chrysophanol, Fig. (**3**) and aloe-emodin, Fig. (**2**)) were effective in *Helicobacter pylori* inhibition [289]. Two of these natural anthraquinones, aloe-emodin and rhein, elicited dose-dependent growth inhibition in *Helicobacter pylori* cultures collected from peptic ulcer patients [290,291]. Additionally, rhein has been shown to inhibit indomethacin-induced gastric ulceration in rats [292]. More recently, a novel natural anthraquinone, a benzo[α]anthraquinone which also showed selective anti- *Helicobacter pylori* activity, has been isolated [293].

Several investigations have also demonstrated the hepatoprotective activity of some naturally-occurring anthraquinones. For example, aloe-emodin, Fig. (**2**) one of the active constituents contained in medicinal plants such as *Aloe* spp., appears to have some protective effect on acute liver injury induced by carbon tetrachloride [294]. Other studies reported the hepatoprotective effect of the anthraquinone emodin on hepatic fibrosis in rats. The emodin-treated rats showed improved liver functions and reduced degrees of fibrosis [295].

Several investigations have reported the ability of some natural quinones to be therapeutically useful as hypolipidemic agents. Both experimental and clinical studies have indicated that a novel source of dietary fibre produced from rhubarb is potentially hypolipidemic. The increased excretion of bile acids and induction of cholesterol 7α-hydroxylase activity may account for

the hypocholesteroelemic effect of rhubarb fiber [296]. Anthrones have been shown to be naturally occurring competitive inhibitors of adenosine-triphosphate-citrate lyase, which is a liver enzyme that catalyzes the cytosolic formation of acetyl-CoA. This reaction provides the major source of acetyl-CoA for fatty acids and cholesterol biosynthesis; thus inhibition of this enzyme offers a potentially unique way to control plasma cholesterol and triglyceride levels. Oleynek *et al.* [297] present evidence for 2-chloro-1,3,8-trihydroxy-6-methyl-9-anthrone as a specific and competitive inhibitor of adenosine-triphosphate-citrate lyase, and might prove very useful as a tool for the discovery of selective mechanistically novel hypolipidemic agents.

Several studies have explored the anti-platelet effect produced by naturally occurring quinones. For example, the quinone fraction isolated from *Auxemma oncocalyx* (Allem/Eo) is a reversible and concentration-dependent inhibitor of human platelet aggregation induced by ADP, arachidonic acid, collagen and thrombin [298]. Zhang *et al.* [299] studied the antiplatelet effects of 2-chloro-3-(4-acetophenyl)-amino-1,4-naphthoquinone. This compound significantly inhibited the collagen-, thrombin-, arachidonic acid- and calcium ionophore A23187-induced aggregation of washed human platelets. These investigations suggest that the antiplatelet activity of this naphthoquinone may be mediated by inhibition of cytosolic calcium mobilization, enhancement of AMPc production and inhibition of ATP secretion in activated platelets. A number of antiplatelet quinones, such as two new series of 2-arylmethyl-1,4-benzoquinones are being synthesized [300].

Various antiplatelet drugs, including quinones, are being investigated as potential treatments for cardiovascular diseases because of their ability to prevent excessive platelet aggregation. For example, Kim *et al.* [301] investigated three naphthoquinones (2,3-dimethoxy-1,4-naphthoquinone, menadione and 1,4-naphthoquinone) for their abilities to inhibit platelet aggegation and to deplete glutathione and protein thiols. These results suggest that quinones that deplete glutathione in platelets demonstrate a marked anti-aggregative effect. Yim *et al.* [302] also reported the myocardial protective effect of an anthraquinone-containing extract of *Polygonum multiflorum* L. The more complete myocardial protection afforded for this extract may be related to its activity to sustain the glutathione antioxidant

status under the condition of ischemia-reperfusion-induced oxidative stress. Additionally, protykin, an all-natural standardized extract of trans-reverastrol and the anthraquinone emodin, Fig. **(4)** derived from the dried rhizome of *Polygonum cuspidatum* Sieb & Zucc. can provide cardioprotection, presumably by virtue of its potent free radical scavenging activity [303].

Various constituents isolated from plants, including quinonic compounds, have been shown to possess antihypertensive and spasmolytic activity. For example, naphthoquinones such as juglone, Fig. **(10)**, 7-methyljuglone and plumbagin, Fig. **(11)** showed a calcium-channel blocking activity in an *in vitro* guinea pig papillary muscle model [304]. Saleem *et al.* [305] reported the hypotensive effect of aloe-emodin, Fig. **(2)** and aloin A, two anthraquinonic compounds isolated from *Aloe barbadensis* Miller. One of them, aloe-emodin, has emerged as a potent hypotensive agent. Furthermore, Xu *et al.* [306] observed the inhibition of aloe-emodin on vascular smooth muscle cells in culture after arterial injury.

Recently, Tanaka [307] has reviewed natural quinonic derivatives as candidates for new orally available antidiabetics. The lead asterriquinone B1 was discovered in a fungal extract, and an analog, 2,5-dihydroxy-3-(1-methylindol-3-yl)-6-phenyl-1,4-benzoquinone, was selected by studying various *in vitro* and *in vivo* tests. These studies shed light on the search for new anti-diabetic agents by targeting insulin receptors. Using an ethnomedical-based drug discovery program, two new compounds, pycnanthuquinone A and B were isolated from the African plant *Pcynanthus angolensis* Llamba and were tested using a diabetic mouse model. The antihyperglycemic actions of these compounds were associated with significant decreases in plasma insulin concentrations, suggesting that both lowered glucose by enhancing insulin-mediated glucose uptake. Pycnanthuquinones A and B are the first representatives of a novel terpenoid-type quinone skeleton which may represent a new class of compounds of potential use in the treatment of type 2 diabetes [308,309]. It has also been suggested that glucose transport activity is an important modulator of cellular glucose metabolism in messangial cells. Zhu *et al.* [310] demonstrated that rhein, Fig. **(5)**, a natural anthraquinone, could ameliorate the metabolic derangement of the human glucose transporter 1 gene by decreasing glucose uptake. These findings have led us closer to the identification of therapeutic

approaches to abort glucose transporter 1 overexpression in diabetic nephropathy.

Several investigations have reported the ability of some natural quinones to be therapeutically useful in the treatment of asthma. The natural anthraquinone chrysophanol-8-O-β-D-glucopyranoside has potent inhibitory activity on hyaluronidase, a enzyme released from mast cells and passive cutaneous anaphylaxis reactions [311]. Cheng *et al.* [312] described the inhibitory effect of 9,10-anthraquinone 2-carboxylic acid on immunoglobulin E-mediated passive cutaneous anaphylaxis reaction. Furthermore, these compounds are promising for treating allergic diseases with chronic and severe pruritus. Lawsone, Fig. **(12)**, 2-hydroxy-3-(2-hydroxyethyl)-1,4-naphthoquinone and 2,2'-methylenebis(3-hydroxy)-1,4-naphthoquinone inhibited scratching behavior in mice with established dermatitis, and they may be effective for the prevention and treatment of atopic dermatitis [313,314].

PLANT CELL CULTURES AS SOURCES OF QUINONES

Cultured plant cells may serve as sources of the various quinones characteristic of intact plants; in addition, new quinones have been produced in plant cell cultures which are not formed in the corresponding parent plants, while sometimes the cultured cells lack the ability to produce easily detectable amounts of natural quinones. For example, callus tissue of *Aloe barbadensis* grown in the dark produced two new tetrahydroanthracene glucosides: 3,4-dihydro-2,4,8,9-tetrahydroxy-6-methyl-anthracenone-4-glucopyranoside and 3,4-dihydro-2-methoxy-4,8,9-trihydroxy-6-methyl-anthracenone-4-glucopyranoside [315]. The cell suspension of *Cassia angustifolia* (senna) was found to produce chrysophanol, physcion and rhein as anthraquinones and several bianthrones, although no sennosides, strong purgative agents in senna were detected in the cell cultures [316].

Several investigations reported the stimulation of anthraquinone production in suspension cultures of *Cassia acutifolia* Del. by salt stress. Pot culture experiments were conducted using NaCl concentrations to assess their impact on the growth and metabolic changes in this plant [317]. Suspension cultures of *Cassia acutifolia* were also established by transferring callus

tissues derived from root, hypocotyl and cotyledon explants onto medium suppplemented with kinetin and containing increased levels of NaCl. The stress induced by salt NaCl raised anthraquinone content and reduced growth of cultures. Furthermore, the salt stress tended to affect more drastically the productivity of anthraquinones in hypocotyl and cotyledon cell cultures than in root cultures [318,319].

With a few exceptions, the characteristic problem of cultivation of plant explants in *in vitro* cultures is a low production of secondary metabolites by these cultures. One of the methods which can achieve an increase in the production of natural substances in *in vitro* cultures, is elicitation of cell cultures with biotic elicitors. For example, hairy root cultures of *Cassia obtusifolia* L. clones transformed with *Agrobacterium rhizogenes* strain 9402 were established to investigate anthraquinone production. It was found that changes of the elements in the culture medium and the addition of rare earth element Eu^{3+} can greatly influence the contents of free anthraquinones in the hairy root [320].

Hairy root culture of the medicinal plant *Rheum palmatum* was established by genetic transformation with *Agrobacterium rhizogenes* and the effects of various media with different pH on growth of the hairy roots and biosynthesis of free anthraquinones were investigated. Cultivation with auxin activated hairy root growth but inhibited the biosynthesis of free anthraquinones [321]. Tomova and Dusek [322], investigated the effect of linoleic acid on the production of anthracene derivatives in *Rheum palmatum* culture *in vitro*. In the elicitation of the culture, the highest response in the production of anthraquinones was observed in linoleic acid in a concentration of 1 mg/ml. Furthermore, the effect of the biotic elicitor *Pseudomonas aeruginosa* in the form of a homogenate and an aqueous suspension of dead cells on the production of anthracene derivatives by the tissue culture of *Rheum palmatum* of a different age and origin was examined. The culture, newly derived from the root of the intact plant, responded to elicitation more sensitively than the culture derived from the seed; nevertheless the content of anthracene derivatives was lower than in the several year old culture [323,324]. More recently, Sepehr and Ghorbanli [325] have studied the effect of nutritional factors on the formation of anthraquinones in callus cultures of *Rheum ribes* L., one of the most important varieties of rhubarb in Asiatic

regions. These studies have demonstrated that the growth rate of callus declined with the increased rate of secondary metabolite production. Kovacevic *et al.* [326] investigated the organogenesis and somatic embryogenesis in cotyledon cultures of *Rhamnus catharticus* L. and in zygotic embryo. Production of physcion derivatives was significantly increased in embryogenic calluses compared to zygotic embryos, but the emodin content was lower than in zygotic embryos.

Plants and their derived cells and tissue cultures in the family Rubiaceae accumulate a number of anthraquinones [327]. One of the aims of the research into the formation of secondary compounds by plant cell cultures is their industrial-scale production. To enhance the productivity of anthraquinone colorants during madder (*Rubia tinctorum*) cell cultures, Shim *et al.* [328] investigated the effects of permeabilizing agents on the production of anthraquinones. Addition of Tween 80 increased the total and released concentrations of anthraquinones. In addition, anthraquinone production was increased by simultaneous use of Tween 80 and chitosan. The effects of auxines and different conditions of illumination on the growth rates of tissue cultures of *Rubia tinctorum* were also studied with regard to the production of anthraquinones. The cultivation of selected callus in medium containing kinetin in the dark showed the best result for the production of anthraquinones, and in the light, the best growth of cultures [329]. More recently, Boka *et al.* [330] have investigated the effect of two elicitor types prepared from three different fungi on the alizarin content in *Rubia tinctorum* suspension culture. These studies suggest that *Botrytis* elicitor are the most effective. Elicitation of genetically transformed madder roots with methyl jasmonate did not influence the growth of their culture, but resulted in an increase in the anthraquinone content without alteration in the qualitative pigment composition [331]. Similarly, an *Agrobacterium rhizogenes*-mediated transformation system for *Rubia peregrina* L. has been established by co-cultivation of callus cultures or by direct infection of explants with this elicitor. The accumulation of total anthraquinones in transformed roots was found to be approximately two-fold higher than that found in one-year-old field-grown roots. Alizarin was found to be the major anthraquinone in transformed root cultures [332].

Other cultured plant cells may serve as sources of new anthraquinones which are not formed in the corresponding parent plants. The chemical investigation on the cell suspension culture of *Morinda elliptica* yielded eight anthraquinones, two of them, anthragallol-1,2-dimethyl ether and purpurin-1-methyl ether, have not been isolated from the original plant [333]. The effects of medium strategy and mode of operation on growth and anthraquinone production of *Morinda elliptica* cell suspension cultures are described [334-336]. *Morinda citrifolia* (Noni) cell suspension cultures are also capable of accumulating high levels of anthraquinones [337].

Other studies have also demonstrated a remarkable difference in constituents between wild plants and callus tissue or cultured cells. For example, tissue and cell culture of *Ophiorrhiza pumila* L. revealed the presence of 11 anthraquinones, including two new ones not present in the parent plant [338]. New compounds of anthraquinone type were also isolated from *Isoplexis isabelliana* (Webb) Masf, *Fusarium oxysporum* L. and *Cruciata glabra* (L.) Ehrend cell suspension cultures [339-341].

A suspension culture of *Cinchona robusta* How, which under normal culture does not produce anthraquinones, produces a range of these compounds after elicitation. Eight new anthaquinones (robustaquinones A-H) were identified, in addition to two known anthraquinones [342,343]. Treatment of *Cinchona robusta* cell suspension culture with a homogenate of *Phytophthora cinnamomi* resulted in cessation of growth and a rapid induction of the biosynthesis of anthraquinones. The strongest induction of anthraquinone production was obtained when the elicitor was added in the early growth phase of the growth cycle [344].

Cultured plant cells may also serve as sources of various naphthoquinones and benzoquinones, whether or not they are present in the whole plants. For example, suspension cultures of *Panax ginseng* C. A. Meyer were treated with either an elicitor preparation from the phytopathogenic *Botrytis cinerea* or a yeast elicitor preparation, and the accumulation of a new compound (2,5-dimethoxy-1,4-benzoquinone), which was not detected in non-elicited cultures, was observed [345]. Induction of naphthoquinone formation in *Impatients balsamina* cell cultures was achieved by using parent plants yielding high levels of 2-methoxy-1,4-naphthoquinone as initiated explants. The cell cultures were capable of producing two naphthoquinones, lawsone

and an unknown compound, which was more polar than lawsone [346]. From the shoots of *Drosera gigantea* L. propagated under *in vitro* cultures, the rare naphthoquinone glucosides droserone (3,5-dihydroxy-2-methyl-1,4-naphthoquinone) and 8-hydroxy-droserone 5-glucosides, together with free naphthoquinones droserone, 8-hydroxy-droserone and plumbagin were isolated. Of the other naphthoquinones typical for the familiy Droseraceae, only hydroxyplumbagin glucoside could be detected, whereas the presence of 7-methyl-juglone and rossoliside (7-methyl-hydrojuglone glucoside) was excluded [347]. Droserone contents are also reported in *in vitro* cultured plants and cell suspensions of *Drosera capensis* L., *Dionaea muscipula* Ellis ex L. and *Triphyophyllum peltatum* Hutch [348-350]. The methanolic extracts of *Drosera rotundifolia* L. and *Drosera spathulata* H. R. obtained by *in vitro* micropropagation, yielded the new pigment 2-methyl-naphthazarin 5-glucoside [351].

Successful commercialisation of the formation of the secondary compounds by plant cell cultures has been achieved by the production of shikonin pigments from plant cell cultures of *Lithospermun erythrorhizon* S. Hwang by Mitsui Petrochemical Industries Ltd. Several studies have investigated factors influencing shikonin production in cultured cells. For example, studies were conducted with a BK-39 callus culture of *Lithospermun erythrorhizon*, which produced seven shikonin derivatives. Selected BK-39 cultures produced almost the same profile of shikonin naphthoquinones as the initial culture [352].

Furthermore, use of *Hypericum perforatum* has increased recently due to the pharmaceutical potential of the naphthodianthrone hypericin found in its leaves. Hypericin has been reported to effect a natural treatment for mild and moderate depression. Bais *et al.* [353] have recently developed a novel cell culture system for *in vitro* growth and production of this species, suggesting a possible technology for large-scale production of hypericin. Light and dark conditions, with cell aggregate size, played important roles in growth and hypericin production in cell suspension cultures. Previously, Kirakosyan *et al.* [354] investigated shoot organ cultures from callus derived from anthers of *Hypericum perforatum* flowers and the effect of several elicitors on the production of hypericins. Pectin and β-1,3-glucan slightly stimulated pseudohypericin production, but had no effect on hypericin production.

Finally, the stimulating effect of cork pieces on hypericin and pseudophypericin production in cells of shoots regenerated from the callus cultures of *Hypericum perforatum* has also been reported [355].

ABBREVIATIONS

DMNQ = 5,8-Dimethoxy-1,4-naphthoquinone
TPA = 12-*O*-Tetradecanoylphorbol-13-acetate
TNF-α = Tumor necrosis factor-α
LPS = Lipopolysaccharide
NO = Nitric oxide
PGs = Prostaglandins
COX-2 = Cyclooxygenase-2
iNOS = Inducible nitric oxide synthase
JNK = Jun N-terminal kinase
HIV = Human immunodeficiency virus
AIDS = Acquired immunodeficiency syndrome
RNase H = Ribonuclease H
RT = Reverse transcriptase
HSV-1 = Herpes simplex virus type I
HCMV = Human cytomegalovirus
5-HT = Serotonin
NA = Noradrenaline
DA = Dopamine
GABA = γ-Aminobutyric acid

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