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The Pharmacological and Pesticidal Actions of Naturally Occurring 1,8-dihydroxyanthraquinones Derivatives

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Abstract The purpose of this work was to assess the various pharmacological and pesticidal actions of 1,8-dihydroxyanthraquinones derivatives (1, 8-DAD) isolated from medical plants to find relationship between their pharmacological and pesticidal activities and their chemical structures to obtain new aspects in pharmaceutical and agricultural practices. A review was done for many studies related to the pharmacological and pesticidal activities of 1,8-DAD isolated and separated from medicinal plants during the last 25 years. 1,8-DAD inhibit many enzymes such as lipase, elistase, arylamine N-acetyl transferase, monoaminooxidase A and B …etc. 1,8-DAD have antimicrobial and pesticidal activities that could be ascribed to their inhibiting activity on some enzymes. Some dermatological diseases could be treated by 1,8-DAD. They have anti inflammatory, anti ulcerogenic activities. 1,8-DAD were capable of inhibiting cellular proliferation, induction of apoptosis and prevention of metastasis. Also, they have applications in psychotherapy as antidepressant agents. Variations in pharmacological and pesticidal actions of 1,8-DAD depend upon their chemical structure. 1,8-DAD have various actions that could open a new aspects to utilize them in pharmaceutical and agricultural practices to develop drugs and pesticides for treating serious pests that attack both human and plants.

Key words: Medicinal plants · Pharmacological actions · Pesticidal activites · 1,8-dihydroxyanthraquinones

INTRODUCTION

1,8-Dihydroxyanthraquinone derivatives (1,8 DAD) are naturally occurring compounds that have been isolated and separated from various medicinal plants, which belong to various botanical families such as Rhamnaceae (buckthorn, cascara), liliaceae (aloe), polygonaceae (rhubarbs) and Caesalpiniaceae(senna). For along period of time the therapautic uses of 1,8 DAD were limited as laxatives [1-10], While over the past 25 years a large number of scientific studies have been conducted to investigate the pharmacological and pesticidal actions of naturally occurring 1,8-DAD. In this review, we would like to discuss the following aspects concerning the 1,8 DAD:

- The chemical structure
- Pharmacological activities
  - Laxative activity
  - Inhibition of enzymes
  - Antimicrobial Activity
  - Antiulcerogenic and Spasmolytic Activity
  - Antiinflammatory, Anti-arthritic, Anti-rheumatic and Anti-oxidant Activity.
  - Cytotoxic and Anti-tumor Activity
  - Antidepressant Activity
- Pesticidal activities
  - Fungicidal activity
  - Insecticidal activity

Chemical Structures: 1,8-DAD, which is derived from anthracen, found in plants in the form of aglycons and glycosides. They have variable degrees of oxidation (anthrones, anthranols, anthraquinones) (Fig. 1) [1, 3, 4, 5, 6,11,10].

Pharmacological Activities

The Laxative Activity: The laxative activity of 1,8-DAD depends upon their structures . The most interesting derivatives are the O-glycosides of dianthrones and anthraquinones, as well as the C-glycosides of anthrons (1,8-DAD without a-CH2-in the 10-Position). Effective dose DE 50 of sennosides, aloe-emodin and chrysophanol are 15, 60 and 500 mg/kg, respectively [4, 5, 6, 12].

The activity of the glycosides of monomeric anthrons is excessive, while the activity of free aglycones is very low [4, 13, 14].

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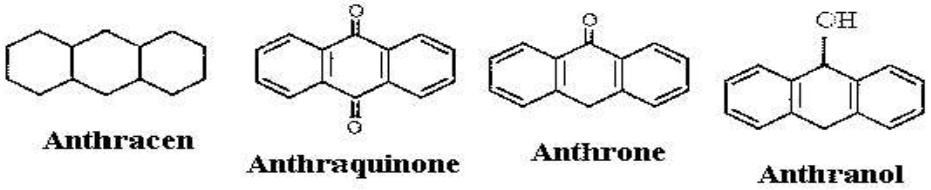
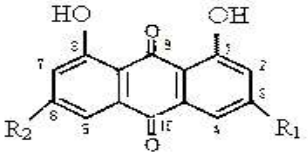
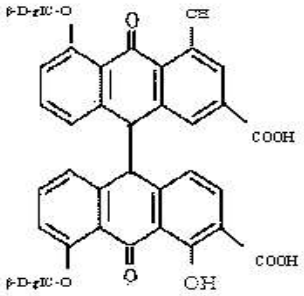
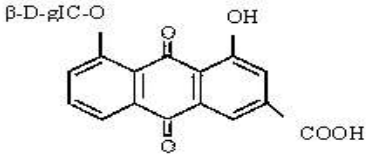
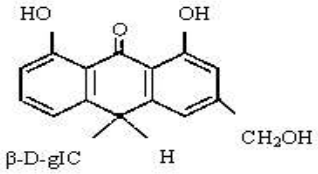


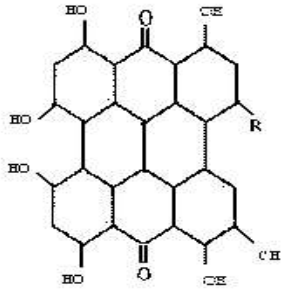


R_1=H , R_2=H : 1,8- dihydroxy an thraquinone.
R_1=CH_3 , R_2=H : Chrysophanol .
R_1= COOH , R_2= H : Rhein .
R_1=CH_3 , R_2=OH : Emodin .
R_1= CH_2 OH , R_2 = H : Aloe – emodin .









R=CH3 , Hypericin
R=CH2OH , Pseudohypericin

Fig. 1: Derivatives of anthracen

Table 1: The inhibiting Action of 1,8-DAD on enzymes

1,8-DAD Compound	Inhibited enzymes	Ref
Aloe emodin	Kallikrein, Elistase, Lactic dehydrogenase, N-acetyl transferase, malic dehydrogenase,penicillase.	[16, 78, 79, 27, 80]
Emodin	Kallikrein, Lipase, Trypsine, Lactic dehydrogenase, Malic dehydrogenase, Xanthinoxidase, Protein tyrosine kinase, Casein Kinase, Arylamine N- acetyltransferase, Penicillase,	[16, 8, 78, 79, 36, 27, 17]
Hypericin	Monoamino oxidase (weak inhibition), Protein kinase C, Telomerase, Dopamine beta hydroxylase, Reverse transcriptase.	[19, 81, 38, 52, 54]
Rhein	Kallikrein, lacticdihydrogenase, Arylamine N acetyltransferase, Penicillase.	[16, 78, 20]

Table 2: The antimicrobial activities of 1,8-DAD

Anthraquinone compound	The inhibited Pathogenic microorganisms
Alcoholic extract of *Cassia alata*	*Staphylococcus aurues, Proteus vulgaris, Eschiseria Coli, Klebsilla acrogens, Pseudomonas auroginosa, Proteus vulgaris* [82].
Aloe-emodin	Herpes simplex viruses (HSV-1, HSV-2), Varicella-ZocterVirus, Pseudorabis Virus, Influenza Virus, Methicillin-resistsnt *Staphylococcus aurues, Helicobacter pylori, Candida albicans, Cryptococcus neoformans, Trichophyton mentagrophytes, Asperigillus fumigatus, Bacillus subtilis* [83, 84, 85, 80, 86, 22].
Chrysophanol	*Candida albicans, Cryptococcus neoformans, Trichophyton mentagrophytes, Aspergillus fumigatus,* Polivirus type 2 and type 3 [85, 87].
1 ,8 -Dihydroxy anthraquinone	*Clostridium perfringens, Staphylococcus aurues* [23].
Emodin	Methicllin-resistant *Staphylococcus aurues, Cytomegale Viruses, Herpes simplex* (HSV-1, HSV-2), *Helicobacter pylori, leishmania donovani, Tryptonosoma spp., Plasmedium falciparum, Bacillus subtilis, Basidiomycete fungus, Fomes annossu* [84, 85, 22, 23, 88].
Hypericin	Herpes simplex (HSV-1, HSV-2), Vsicular stomatitis viruses, para influenza Vaccina Vruses, HIV, Human papimola viruses (HPV-1, HPV-6, HPV-11, HPV-16, HPV-18), Methicillin resistant strain of *Staphylococcus aureus, Helicobacter pylori, Bacillus subtilis, Bacillius cereus* [89, 90, 91, 92, 93].
Physcion	Herpes simplex viruses (HSV-1, HSV-2), Cytomegale viruses, *Candida albicans, Cryptococcus neoformans, Trichyophyton mentagrophytes, Aspergillus fumigatus* [85].
Preperation from Radix of *Rumex acetosa*	*Trichophyton, Microsporum, Staphylococcus aurues, Pseudomonas aeruginosa* [57].
Rhein	Methicillin-resistant *Staphylococcus aureus, Candida albicans, Cryptococcus neoformans, Trichophyton mentagrophytes, Aspergillus fumigatus. Helicobacter pylori, Bacillus subtilis, Bacteroides fragilis, Nesseria gonorrhea, Streptococcus viridians* [84, 85, 81, 23, 94, 26].

Table 3: The inhibited tumor cell lines by 1,8-DAD

1,8-DAD compound	Inhibited tumor cell lines
Aloe-emodine	Human lung squamous cell carcinoma, Human oral squamous cell carcinoma (HSC-2), Salivary gland tumor (HSG) cell lines, Human gingival fibroblasts (HGF), Human heptaoma cell lines, Merkel carcinoma cell lines , Neuroctodermal tumor, Human promyelocytic leukemia HL-60 cells, P388 leukemia(in mice) [27, 49, 94, 41, 42, 95, 44, 47].
Chrysophanol	Human non-small lung tumor cell lines, SK-OV-3 human ovary tumor cell lines,SK-MEL-2 melanoma ,XF 498 central nervous system tumor cell lines [49].
Emodin	Human oral squamous carcinoma cell line (HSC-21), Salivary gland tumor (HSG) cell lines, Human gingival fibroblasts (HGF), HER-2/over expressing human breast cancer cells, ,P388 leukemia (in mice), Human lung squamous carcinoma cell line, Prostate cancer cells [37, 49, 94, 47, 47].
Hypericin	Human mamalian leukocytes, Pituitary adenoma cell lines, Nasopharyngeal carcinoma,leukemia K562 and U937 cells , Brain glioblastoma cells LN 229-A-549 [96, 38, 97].
Physcion	A549 non-smal human lung cell lines, SK-OV-3 human ovary tumor cA549 non-smal human lung cell lines, SK-OV-3 human ovary tumor cell lines,SK-MEL-2 melanoma,XF498 human central nervous system cell lines, HCY 15 Colon tumor cell lines [49].
Rhein	Ascites cancer, Sarcoma-180, Human cervical cancer caski cells, Human glioma cells [98, 39, 48].

The mechanism of action of 1,8-DAD as stimulant laxatives could be explained by one or more of the followings:

- In past, 1,8-DAD were thought to act by irritation of the mucosa which lead to increasing of motilitay of intestinal tract [4].
- Regarding to sugar components, the anthraquinone glycosides and dianthrones are polar molecules, water soluble and have a high molecular weight, so they are not resorbed nor hydrolyzed in the small intestine. In the colon, they are hydrolyzed by ß glucosidases of the intestinal micro flora and the freed anthraquinones are in a reduced from, whereas the reduced forms affect intestinal motility [4,13]. It has been shown, *in vivo*, that rhein anthrone acts by direct contact with the epithelial cells of intact intestinal mucosa [14] 1,8-DAD inhibit the growth of anaerobic *Bacteroides fragilis*. The toxins of *B. fragilis* inhibit the motility of the intact intestinal mucosa [15].

1,8-DAD inhibit the Na-K ATPase activity of enterocytes which affect the absorption of water and electrolytes. They induce an inhibition of water, sodium and chloride resorption and an increase in the secretion of potassium by the intestinal mucosa [6, 12, 14].

The laxative potential activity of anthraquinone glycosides in comparison to their aglycons could be ascribed by that sugars in anthraquinone glycosides molecules could act as transporters by preventing the active moiety from being absorbed prior to being freed in the colon under the influence of bacterial enzymes [4].

Inhibition of Enzymes: The increase in the level of some enzymes associates with some diseases. For example the lipase's level increases in case of acute pancreatitis, peritonitis, perforated peptic ulcer,…etc. On the other hand it was observed that 1,8-DAD inhibit various enzymes. The inhibited enzymes by 1,8-DAD are shown in Table 1. Chrysophanol and physcion have no inhibition action on kallikrein, trypsine, lipase and elistase [16] Physcion and emodine-8-0-ß-D glucoside can not inhibit protein tyrosine kinase in comparison with emodine, the most strong inhibitor [17]. The presence of hydroxyl group at the 6-and 8 positions is an important factor behind its inhibition activity. The values of inhibiting activity (I_{50}) of 1,8-DAD are variable depending upon the presence of hydroxyl group in ortho-position. The I_{50} of emodine on Kallikrein, trypsin and lipase is 31.5 40.5 and 46.5 mcg/ml respectively, whereas the I_{50} of Aloe-emodin and rhein on kallikrein are 38.5 and 26.0 mcg/ml [8, 16].

The Antimicrobial Activity of 1,8-DAD: The 1,8 -DAD or crude extracts containing them have antimicrobial activity. They have antibacterial, antiviral, antifungal and antiprotozal activity. The antimicrobial activity of 1,8-DAD are shown in Table 2. The antimicrobial activity of 1,8-DAD is related to their inhibition activity on the enzymes which are necessary to microorganisms. Penicillase is inhibited by rhein, emodin and aloe-emodin [18]. HIV-1 reverstranscriptase is inhibited by hypericin [19]. The activity of N-acetyltransferase in *Helicobacter pylori* decreases with increasing levels of rhein [20]. 1,8-DAD exhibit antibacterial activity by inhibiting nucleic acid synthesis [21].

The antimicrobial activity of 1,8-DAD against some strains of bacteria depends upon their chemical structures. Rhein> emodin> 1,8-dihydroxyanthraquinone in decreasing order, inhibit the growth of *Staphylococcus aureus* [22, 23]. However, the anti-bacterial activity of oxidized 1,8-DAD decreased when they changed to their reduced forms [1, 8]. The 1,8 -DAD are phenolic compounds containing hydroxyl group in various positions of anthraquinone molecule, so that they exhibit a various degree of inhibiting activity on the microbial growth and on that enzymes necessary to their metabolic process.

Anti Ulcerogenic and Spasmolytic Activity: As 1,8-DAD have an action on the gastrointestinal tract as laxatives, they have anti ulcerogenic and spasmolytic activities. Emodin from *Rhamnus triquirta* in dose of 15 mg/kg has anti ulcerogenic effect. It decreases the production of HCl and pepsin and increases the production of mucosa [24-26] The anti ulcerogenic activity of 1,8-DAD could be ascribed to their inhibition activity on arylamine N-acetyltranseferase. Aryl amine N-acetyltranseferase is an important enzyme to the growth of *Helicobacter pylori.* However, this enzyme was reported to be inhibited by emodine, aloe-emodine and rhein [27, 20, 21]. 1,8-DAD have spasmolytic activity. Chrysophanol at concentrations of 5 and 10 mcg/ml has papavarin-resemble spasmolytic activity whereas emodin and physcion at the same concentrations have very weak action [24].

Anti Inflammatory, Anti Arthritic, Anti Rheumatic and Anti Oxidant Activity: Emodin at concentration of 15 mg/kg in laboratory animals showed strong anti-

inflammatory activity [25]. Research has been directed at the long-term treatment of ostoarethrites using rhein. The diacetylated form of rhein showed antiinflammatory, antipyritic and analgesic activities and can be used for treatment of arithrites [28, 29]. Emodin as antioxidant properties, aloe-emodin and rhein scavenge reactive oxygen and free-radical species and they are arranged in the following decreasing order, emodin>rhein>aloe-emodin, which explain the activity of 1,8-DAD as antioxidants [30-32]. As other phenolic compounds, the antioxidant activity is due to the presence of hydroxyl groups in their structure. The two hydroxylgroups arranged at either the *meta* or *ortho* positions are required for an anthraquinone to inhibit lipid peroxidationin in rat heart mitochondrial system. However, anthraquinone derivatives that have no hydroxyl groups as well as two hydroxyl groups affixed to different rings did not inhibit lipid peroxidation .The anti oxidant activities may relevant to the C-ring double bond and the *ortho*-dihydroxyl and a number of hydroxyl groups [30, 31].

Cytotoxic and Antitumor Activity: In the last 20 years, the interest in naturally occurring 1,8-DAD as cytotoxic agents was increased. Also, the synthetic analogues of 1,8-DAD showed inhibition activity to the growth of carcinogenic cells [33-35]. The most abundant anthraquinones were capable of inhibiting cellular proliferation, induction of apoptosis and prevention of metastasis. These capabilities are reported to act through tyrosin kinases, phoshoinositol 3-kinase, protein kinase C (PKC), mitogen activated protein kinase (MAPK) singling cascades and other enzymes [17, 36-40].

The anti proliferative properities of some 1,8-DAD such as aloe-emodin has been demonstrated to be achieved through the p53 and its downstream p21 pathway. Rhein could effectively inhibit the uptake of glucose in tumor cells, causing changes in membrane-associated functions and leads to cell death [40-42]. Extract of formosan *Rhamnus* species containing emodin, physcion, chrysophanol and nakahalene has cytotoxic activity [43]. Emodin, Aloe emodine, chrysophanol and rhein in individual cases show cytotoxic activity [44, 45, 34]. Aloe emodine from leaves of *Knipholia foliosa* has anti leukemic activity [46, 47]. Emodin and rhein inhibit the growth of melanome at a percent of 76%. The breast cancer cells in athymic mice were inhibited by emodin which sensitizes these cells to the Paclitaxel [37] while rhein improves the therapeutic index of adriamycine [48].The inhibited tumor cell lines by 1,8-DAD are shown in Table 3. 1,8-DAD have various cytotoxicity actions depending upon their chemical structures. The cytotoxicity of (1) chrysophanol, (2) physcion, (3) emodin,and (4) emodin-8-O-β -D-glucopyronoside, against five cultured human tumor cell lines was investigated. Among the tested compounds, emodin showed the potent cytotoxic activities against all tumor cell lines. Chrysophanol and physcion were less cytotoxic than emodin. Emodin possesses a OH-group at C-6 position differently from compounds 1 and 2. This group may play an important role for its cytotoxicity. On the other hand, compound 4 contained a OH-group at C-6 position as emodin, however, Compound 4 showed the lowest activity, which suggest that the additional OH-group at C-8 is necessary for their cytotoxicities. It was found that the cytotoxic activity of oxidized 1,8-DAD is more active than reduced forms [49, 35].

Antidepressant Activity: 1,8-DAD showed an inhibition activity on central nervous system, from which emodin has antidepressant activity [49]. Hypericin, pseudohypericin, which are biogenetically derived from emodin anthrone, are the most constituent of Saint John's wort SJW plant (*Hypericum perforatum* L) standardized extract, which are used successfully to treat mild to moderate depression at dose 300-900mg/day [50, 51]. In 2000, Amaricans spent about $200 million for St. John's wort and 1.5 million people in the united state used it on regular basis. Use of St. John's wort is even more significant in Europe, especially in Germany [51, 52].

The mechanism of action has not been clearly defined, *in vitro* SJW extract inhibits serotonin, norepinepherine, dopamine, gamma-amino butyric acid A(GABAA) and gamma-amino butyric acid B(GABAB)[53]. It has been stated that hypericin has a weak inhibition activity on monoaminoxidase (MAO), and dopamine betahydroxylase [19, 54]. Emodin showed potent inhibition activity on the MAO A and B [55].

Anti Psoriatic Activity: Patents and studies show that 1,8-DAD or medicinal herbs containing them have therapeutic activity for treatment of various dermatological diseases such as psoriasis and dermatitis [56]. Preparations from roots of *Rumex acetosa* are used for treatment of fungal and bacterial dermatological diseases caused by *Trichophyton spp*., *Microsporum spp*. and *staphylococcus aeruginosa* [57]. Gels, ointments and lotions containing the extracts of *Aloe vera* as the main ingredient are used successfully to treat wounds, insect bites, sun burns, chaps and psoriasis [50, 58]. Dithranol is the International Nonproprietary Name of (Anthralin), the

1,8-Dihydroxyanthron, which is widely used in the treatment of psoriasis is derived from a natural compound called chrysorobin which is prepared from the araroba tree (*Andira araroba*).

Psoriasis could be treated by using composition derived from roots of *Asphodelus microcarpus* including 3-methyl anthraline, chrysophanol,and aloe-emodine [59].

Mechanism of action of anthralin still uncertain and results characterizing its activities are controversial. Over several years of research, it has been reported that anthralin inhibits glycolytic key enzymes involved in epidermal proliferation such as glucosephosphate dehydrogenase (glucose-6-phosphate dehydrogenase), 5-lipoxygenase and glyceraldehdrogenase. Other researchers have shown that under certain conditions, anthralin may have anti proliferative as well as anti respiratory activity in a human transformed epidermal keratinocyte line or in skin fibroblasts in culture. Alternatively, modulation of the cellular redox status or effects on mitochondoria and immune cells, such as neutrophills, macrophages, langerhans cells and lymphocytes have been shown to be sensitive to this compound [60-64].

Anthraquinones as Botanical Pesticides: Several drawbacks to the use of synthetic pesticides do exist, however and some principally from these substances deleterious affects, both immediate and cumulative by time on the environment. That is, many synthetic pesticides are extremely persistent in the soil (i.e., do not biodegrade easily) and build up high residue levels as repeated seasonal applications are made.

Insecticidal Activities: The feeding-deterrent property is an important function of emodin in mediating plant-animal interactions. Emodin has a deterrent effect on a large spectrum of organisms from invertebrates to vertebrates. In relatively low concentrations of emodin, gypsy moth (*Lymantria dispar*) larvae reduced feeding and prolonged development and with high concentrations and consequently pronounced mortality occurred in 2-3d [65]. The mode of action of emodin as an insect antifeedant is yet to be studied.

The effective feeding deterrent property of emodin to phytophagous insects was suggested as an explanation for the little insect attack of *Rhamnus alnifolia* foliage [65]. The number of species of phytophagous insects on introduced *Rhamnus cathartica* plants in Canada is much lower than on native plants in Europe [66]. This may be indirect evidence of the importance of emodin (as well as other anthraquinones), which occurs in *R. cathartica* leaves [67], in the evolution of plant defense against phytophagous insects. A long coevolution period in Europe, but not in Canada, may enable the insects to penetrate the defensive properties of *R. cathartica.* This is based on the assumption that a long history of association between certain groups of insects and plants caused a progressive accumulation of adaptations enabling insects to tolerate feeding deterrents [68].

Plant Antimicrobial Activities: Many plant secondary metabolites of many plants have an allelopathic effect on microorganisms [69]. Surprisingly, it is unclear whether phenols and other secondary metabolites have a role in protecting plants from disease *in vivo* [70]. But it has been demonstrated that anthraquinones, extracted from different species of *Aloe*, exhibit antibacterial activity by inhibition of nucleic acid synthesis in *Bacillus subtilis* [21]. For many years it has been known that emodin has direct antibacterial activities [71, 72]. Emodin was found to inhibit nine soil bacterial species (*Arthrobacter globiformis*, *Chlorella pyrenoidosa*, *Bacillus megaterium*, 4 *Rhizobium* spp. and *Azotobacter chroococcum*) *in vitro* with minimal concentrations of 10-200 μg ml^{-1} [73]. In the presence of emodin, the cells of these bacteria developed aberrant morphological forms, especially enhanced length [73].

Emodin was also found to be an efficient antifungal toxin. Emodin isolated from *Rhamnus triquetra* bark was highly effective against spore germination of 17 tested fungi species (including seven species of *Alternaria* and three species of *Fusarium* [74]. Less than 50% inhibition of the spores of all fungi species was achieved at an emodin concentration of 500 μg ml^{-1} and maximum inhibition (up to 100% in some species) was observed at an emodin concentration of 2000 μg ml^{-1} [74]. Emodin has also highly inhibitory effect against a pathogenic basidiomycete fungus, *Fomes annosus* [75].

From the plant perspective, several direct and indirect nonexclusive ecological consequences of the antimicrobial activity of emodin are possible. Because plant survival frequently depends upon its disease resistance [76], emodin may directly render the plant resistant to disease caused by microbial pathogens. It seems that emodin is a preinfection toxin because it is consistently present in the plant [77] and no study has indicated that it increases subsequent to infection as an inducible defense. Recently Singh *et al*. [74] suggested that the ability of some higher plants to resist fungal pathogens depends on the presence of emodin along with

other chemicals in their tissues. In addition, because emodin inhibits soil microorganisms, which may compete with the plants for inorganic nutrients, emodin may indirectly improve the competitive advantage of plants under some circumstances [69]. On the other hand, emodin may also inhibit some mutualistic soil microorganisms, which are beneficial for their host plants and therefore may reduce plant fitness. This possible trade-off has not yet been studied.

In conclusion, direct evidence of the ecological role of the antimicrobial activity of emodin in plants *in vivo* is limited. However, the *in vitro* studies and other circumstantial evidence indicate that the allelopathic properties of emodin may directly and indirectly affect the survival and growth of plants.

CONCLUSION

Variations in pharmacological and pesticidal actions of 1,8-DAD depend upon their chemical structure. 1,8-DAD have serious actions that could open new aspects to ultilize them in pharmaceutical and agricultural practices to develop drugs and pesticides for treating serious pests that attack both human and plants.

REFERENCES

1. Muzychkena, R.A., 1998. Natural anthraquinones, biological and physico-chemical properites, Phasis, Moscow.
2. Bombardelli, E., G. Pifferi, 1988. Naturally occuring anthraquinone derivatives. Boll. Farm, 127(1): 3-12.
3. Thomson, R.Y. 1987. Naturally occuring quinones recent advances, Chapm. and Hall, London-NewYork.
4. Bruneton, J., 1999. Pharmacognosy, phytochemistry of medicinal plants. 2nd edition.
5. Trease, J.E.T., W.C. Evans, 1989. Pharmacognosy. 12th edition. London.
6. Klaus, E., 1980. The physiological basis of laxative action. Pharmacology, 20(1): 2-20.
7. Abu-darwish, M.S., 2001. Pharmacognostic study of different organs of *Rhamnuus cathartica* and *Rhamnus dispermus*. Ph.D thesis, Ukrainian National Academy of Pharmacy, Ukrain.
8. Zhuravlev, M.S., A.M. Kovaleva, A.N. Komissarenko, T.N. Kryuchkova and M. Abu-darwish, 1999a. Study of the lipotropic activity of natural anthraquinones and their synthetic analogues .News of Pharmacy, 1(19): 29-32.
9. Zhuravlev, M.S., A.I. Pavli, T.N. Kryuchkova and M. Abu-darwish, 1999b.The anthraquinones of some types of rhamnacea family and their biological activity. Collection of scientific works: Contemporary problems of pharmacognosy and phytotherapay. Yaroslavi, pp: 52-54.
10. Zhuravlev M.S., A.I. Pavli, M. Abu-darwish and T.N. Kryuchkova, 1998. Chemical and biological study of phenolic compounds of *Frangula alnus* and *Rhamnus cathartica*. Material of international conference: Theory and practice of development of medicaments. Kharkive-Ukrain, pp: 110-114.
11. Abu-darwish, M., M.S. Zhuravlev and A.I. Pavli, 1998. The chemical study of *Rhamnus cathartica*. The international conference: physiological and biological aspects of study of the medicinal plants. Novosibirsk, Russia.
12. Leng-Peschlow, E. 1986. Dual effect 0f orally administered sennosides on large intestine and fluid absorbtion in the rat. J. Pharm. Pharmacol., 38: 606-610.
13. Westendorf, J., 1993. Anthranoid derivatives General discussion. In: De Smet PAGM, Kellerk, Hansel R *et al*. Adverse effects of herbal drugs, 2, Berlin: Springer Verlay, pp: 105-118.
14. De witte, P. and L. Lemli, 1990. The metabolism of anthranoid laxatives. Hepato-gastroenterol., 37: 601-605.
15. Akao, T., T. Akao, M. Hattori, T. Namba and K. kobashi, 1985. Enzymatic reducation of sennidin and sennoside in peptostreptococcus intermedius. J. Pharmacobio. Dyn., 8(10): 800-807.
16. Cal, Y.N. and Q.H. Chen, 1989. Inhibitory effects of anthraquinone derivatives on four pancreatic enzymes. Acta. Biochem. Biophys. Sin., 12(4): 338-343.
17. Jayasuriya, H., N.M. Koonchanok, J.L. Mclaughlin, R.L. Geahlen, C.J. Chang, 1992. Emodin, a protein tyrosine Kinase inhibitor from *Polygonum cuspidatum*. J. Natur. Prod. 55: 3890-3896.
18. Wen-Li, L., H. Hui-Man, L. Rong-Dih and Wen-chi., 2003. Screening for natural inhibitors of pencillinase by copolymerization of hydrolyzed starch or glycogen in sodium dodecylsulfate polacrylamide gels for detecting pencillinase activity. Bot. Bull. Acad. Sin., 44: 187-191.
19. Kubin, A., F. Wierrani and W. Grunberger, 2005. Hypericine the facts about controversial agent. Current pharmaceutical Design, 11(2): 233-253.

20. Chung, J.G., M.F. Tsou, H.H. Wang, H.H. Lo and S.E. Hsiesh, 1998. Rhein affects arylamine N acetyltransferase activity in *Helicobacter pylori* from peptic ulcer patients. J. Appl. Toxicol., 18(2): 117-123.
21. Levien, H., R. Hazenfrantz, J. Friedman and M. Perl, 1988. Partial purification and some properties of the antibacterial compounds from *Aloe vera*. Phytotherapy Res., 1: 1-3.
22. Fuzellier, M.C., F. Mortier, T. Girard and J. Payen, 1981. Study of antibiotic properities of some anthraquinones using chromatographic microplates Ann. Pharm. Fr., 39: 313-318.
23. Yan-Wen, W., Jie Quyan, X. Xiao-He, G. Wen-Yuan and L. Yi, 2006. Antimicrobial properities and Toxicity of Anthaquinones by microcalorimetric Bioassay. Chinase J. Chem., 24(1): 45-50.
24. Tahir, F.F., F.A. Hussaini and A. Shoeb, 1986. Spasmolytic anthraquinones from *Cassia pumilla*. Fitoterapia, 57(4): 271.
25. Goal, R.K., G.G. Das, S.N. Ram and V.B. Pandy, 1991. Antiulcerogenic and anti-inflammatory effects of emodin isolated from *Rhamnus triquerta*. Indian J. Exp. Biol., 29(3): 230-232.
26. Bae, E.A., M.J. Han and D.H. Kim, 1998. Anti *Helicobacter pylori* activity of herbal medicines. Biol. Pharm. Bull., 21(9): 990-992.
27. Chung, J.G., H.H. Wang, L.T. WU, S.S. Chang and W. Chang, 1997. Inhibitory actions of emodin on arylamine N-acetyl-transferase activity in strains of *Helicobacter Pylori* from peptic ulcer patients. Food Chem. Toxicol., 35(10-11): 1001-1007.
28. Davis, R.H., P.S. Agnew and E . Shpiro, 1986. Anti arthritic activity of anthraquinones found in aloe for podiatric medicine. J. Am. Pod. Med., pp: 61-66.
29. Carcasona, A., W. Grimmimger, H. Zaeske, P. Hictala, K. Wittholn and A.S. Madus, 1993. Verfahren zur Herstellung Von Diacetylrhein. pup. Pat. 4120989. FRG.
30. Hyun, A.J., Y.C. Hae, Y. Takako, C. Youn and K. Sook, 2004. Aalaternin and Emodin with hydroxyl radical inhibitory and / or scavenging Activities and hepato protective activity on Tarcine induced cyto toxicity in Hep G2 cells. Arch. Pharm., 27(9): 953.
31. Main, M., S. Brumelleschi, S. Tarli, A. Rubino, D. Benetti, R. Fantozzi and L. Zilletti, 1987. Rhein: an anthraquinone that modulates superoxide anion production from human neutrophils. J. Pharma. & Pharmacol., 39(10): 845-847.
32. Yen, G.C., P.D. Duh and D.Y. Chung, 2000. Antioxidant activity of anthraquinones and anthrons. Food Chemistry, 70: 437-441.
33. Shii, T., S.I. Keno, S. Kunimoto, T. Kawauchi, T. Ofani and M. Hori, 1997. Inhibition of anchorage-independent growth of tumor cells by IT-62-B a new anthracycline. J. of Antibiotics, 50(10): 853-859.
34. Koyama, M., T.R. Kelly and K. Watanbe, 1988. Novel type of potential anticancer agents derived from chrysophanol and emodin, some structure-activity relationship studies. J. Med. Chem., 31(2): 283-284.
35. Teesdalespitle, P., Y. Gilas, M.R. Craven, K. Ruparelia, P.J. Smith and L.H. Paterson, 1994. Relationship between DNA binding affinity, inhibition of topoisomerase II and cytoxicity of some novel alkylamino-anthraquinone antitumor agents. J. Pharm. and Pharmacol., 46(2): 1063-1067
36. Yim, H., Y.H. Lee, C.H. Lee and S.K. Lee, 1999. Emodin an anthraquinone derivative isolated from the rhizome of *Rheum palmatum*. Selectively inhibits the activity of Casein Kinase as a competitive inhibitor. Planta Med., 65: 9-13.
37. Lisha, Z., L. Yiu-Keung, X. Weiya, N. Gabril, Hortbagyi and H. Mien-Chie, 1999. Tyrosine Kinase inhibitor Emodin suppress growth of HER-2/neu-overexpressing breast cancer cells in athymic mice and sensitize these cells to the inhibitory of paclitaxel. Clinical Cancer Res., 5: 3443-353.
38. Hamilton, H.B., D.R. Hinton, R.E. Law, R. Gopalakrishna, Y.Z. Su, Z.H. Chen, M.H Weiss and W.T. Couldwell, 1996. Inhibition of cellular growth and induction of apoptpsis in pituitary adenoma cell lines by the protein kinase C inhibitor hypericin potential therapeutic application. J. Neurosurg., 85: 329-334 .
39. IP, S.W., Y.S. Weng, S.Y. Lin, Mei-Dueyang, N.Y. Tang, C.C. Su and J.G. Chung, 2007. The role of cat2 on rhein induced apoptosis in human cervical cancer celles. Anticancer Res., 27(1A): 379-389.
40. Qinq, H., L. Guondang, S. Han-Ming, C.M. Maxey, Chung and N.O. Choon, 2006. Anticancer properites of anthraquinones from Rhubarb. Medicinal Research Reviews. Rath, G., M. Ndonzao and K. Hostettmann, 1990. Antifungal anthraquinones from *Morinda lucida* Int. J. Pharmacognosy, 33(2): 107-114.
41. Kuo, P.L., T.C. Lin and C.C. Lin, 2002. The anti proliferative activity of aloe-emodin is through P53-dependant and P21-dependant apoptotic pathway in human hepatoma cell lines. Life Sci., 71(16): 1879-1892.

42. Wasserman, L., S. Avigad, E. Beery, B.J. Norden and E. Fenig, 2002. The effect of Aloe -emodin on the proliferation of anew merkel carcinoma Cell Line. Am. J. Dermatopathol. Feb. 24(1): 17-22.
43. Wei, B., N. Chun and S.J. Won, 1992. Nakahalene and cytotoxic principles of formosan *Rhamnus* species. J. Natur. Prod., 55(7): 967-969.
44. Chan, H.C., W.T. Hsieh, W.C. Chang and J.G. Chung, 2004. Aloe-emodin induced *in vitro* G2/M arrest of cell cycle in human promyelo cytic leukemia HL-60 cells. Food and Chemical Toxicology, 42(8): 1251-1257.
45. Kagedal, K., D. Bironaite and K. Ollinger, 1999. Anthraquinone Cytotoxicity and apoptosis in primary cultures of rat hepatocytes. Free Radic Rec., 31(5): 419-428.
46. Berhanu, E. and E. Dangne, 1984. Aloe-emodin acetate and anthraquinone derivative from leaves of *Knipholia foliosa* . Planta Medica., 50(6): 523-524.
47. Lu, M. and Q.H. Chen, 1989. Biochemical study of Chinese rhubarb, Inhibitory effects of anthraquinone derivatives on p338 leukemia in mice. J. China Pharm. Univ., 20: 155-157.
48. Fanciulli, M., 1992. Inhibition of membrane redox activity by rhein and adriamycin in human glioma cells. Anticancer Drugs, 3(6): 615-621.
49. Nam-Jae, L., C. Jung, K. Byung-Soo, R. Shi-Yong, H. Yeong-Hwan, L. Seung and L. Dong-Ung, 2005. Antimutagenieity and cytotoxcity of the constituents from the Aerial Parts of *Rumex acetosa*. Biol. Pharm. Bull., 28(11): 2158-2161. Nicioka, I., 1983. Pharmcological action of medical plants components, Rhubarb. Med. and Drug J., 19(10): 67-72.
50. Adriane Fugh-Berman, 2003. The 5 Minute Herb and Dietary supplement consult. Lippincott Williams and Wilkins. Philadelphia.
51. Vollmer, J.J. and J. Rosenson, 2004. Chemistry of St. John›s Wort: Hypericin and Hyperforin. J. Chem. Edu., 81(10): 1-9.
52. Fugh-Berman, A. and M. Cott, 1999. Dietary supplements natural products as psychotherapeutic agents. Pasychosom. Med., 61: 712-728.
53. Zanoli, P., 2004. Role of hyperforin in the pharmacological activites of St. John›s Wort. CNS. Drug Rev., 10(3): 203-218.
54. Suzuki, O., Y. Katsumata and M. Oya, 1984. Inhibition of monoamine oxidase by hypericin. Planta Med, 50: 272-274.
56. Coats, B., 1994. Method of processing stabilized *Aloe vera* gel obtaind from the whole *Aloe vera* leaf. Puplished. Pat USA. 5356811.
57. Vatada, U., 1991. Preperation for treatment of skin diseases. Pat. 393723. Japan.
58. Syed, T.A., S.A. Ahmad and A.H. Hetal, 1996. Mangement of psoriasis with *Aloe vera* extract in hydrophilic cream:aplacebo controlled, double-blind study. Trop. Med. Int. Health, 1: 505-509.
59. Moady, 1999. Anti psoriatic composition, method of making and method of using. A61K31/12 USA. Pat 4826677.
60. Mahrle, G., 1997. Dithranol. Clin. Dermatol., 15: 723-737.
61. Peters, B.P., F.G. Weisman and M.A. Gill, 2000. Pathophysiology and treatment of psoriasis. Am. J. Health Syst. Pharm., 57: 645-659.
62. Mendonca, C.O. and A.D. Burden, 2003. Current concepts in psoriasis and its treatment. Pharmacol. Ther., 99: 133-147.
63. Mcgill, A., A. Frank, N. Emmett, D.M. Turnbull, M.A. Birch-Machin and N.J. Reynolds, 2005. The anti-Psoriatic drug anthralin accumlates in keratinocyte mitochondria,dissipates mitochondorial membrane potential and induces apoptosis through a pathway dependent on respiratory component mitochondria. FASEB J., 19(8): 1012-4.
64. Wiegrebe, W. and K. Müller, 1995.Treatment of psoriasis with anthrones-chemical principles, biochemical aspects and approaches to the design of novel derivatives. Skin Pharmacol., 8(1-2):1-24.
65. Trial, H.T. and J.B. Dimond, 1979. Emodin in buckthorn: a feeding deterrent to phytophagous insects. Canadian Journal of Entomology, 111: 207-212.
66. Malicky, H., R. Sobhian and H. Zwölfer, 1970. Investigations on the possibilities of a biological control of *Rhamnus cathartica* L. in Canada: Host range, feeding sites and phenology of insects associated with European Rhamnaceae. Zeitschrift für Angewandte Entomologie, 65: 77-97.
67. Maw, M.G., 1981. *Rhamnus Cathartica* L., common or European buckthorn Biological control programs against insects and weeds in Canada 1969-1980.
68. Bernays, E.A. and R.F. Chapman, 1994. Host-plant selection by phytophagous insects. New York, USA: Chapman and Hall. Bo-Kyung, S., K. Moo-Key, Wang-Hyual., L. Dong-Heon, L. Hoi-Seon, 2004. Growth response of *Cassia obtusifolia* toward Human intestinal bactaria. Fitoterapia, 75(5): 505-509.
69. Rice, E.L., 1995. Biological control of weeds and plant diseases: advances in applies allelopathy. Norman, OK, USA: University of Oklahoma Press.

70. Harborne, J.B., 1993. Introduction to ecological biochemistry, 4th Ed. London, UK. Academic Press.
71. Anke, H., I. Kolthoum and H. Laatsch, 1980. Metabolic products of microorganisms. The anthraquinones of the Aspergillus glaucus group. II. Biological activity. Archives of Microbiology, 126: 231-236. Assoc., 75: 229-237.
72. Kitanaka, S. and M. Takido, 1986. Studies on the constituents in the roots of *Cassia obtusifolia* L. and the antimicrobial activities of constituents of the root and the seeds. Yakugaku Zasshi, 106: 302-306.
73. Le Van, T., 1984. Emodin a fungal metabolite and the effects of emodin on the growth of some soil microorganisms. Acta Agraria et Silvestria Seriea Agraria, 23: 235-242.
74. Singh, U.P., K.P. Singh, S.P. Singh and V.B. Ram, 1992. Effect of emodin isolated from *Rhamnus triquetra* on spore germination of some fungi. Fitopatology Brasileira, 17: 420-422.
75. Donnelly, D.M.X. and M.H. Sharidan, 1986. Anthraquinones from *Trichoderma polysporum*. Phytochemistry, 25: 2303-2304
76. Rice, E.L., 1984. Allelopathy, 2nd edn. Orlando, FL, USA: Academic Press, Inc.
77. Tsahar, E., 2001. The impact of the secondary metabolite emodin in *Rhamnus alaternus* on fruits removal and seed predation. M.Sc. thesis, Tel Aviv University, Israel.
78. Zhang, Y. and Q. Chen, 1986. Biochemical study of Chinese Rhubarb. XIV. Inhibitory effects of anthraquinone derivatives in some NAD-related dihydroginase. Acta Biochem. et. Biophys. Sin., 18(3): 239-245
79. Noro, T., K. Noro, T. Miyase, M. Kuroyangi, K. Umehara, A. Uneo and S. Fukushima, 1987. Inhibition of xanthine oxidase by anthraquinones. Chem. and Pharm. Bull., 35(10): 4314-4316.
80. Wang, H.H., J.G. Chung, C.C. Ho, C.T. Wu and S.H. Chang, 1998. Aloe-emodin effects on arylamine N-acetyl transferase activity in the bacteria *Helicobacter pylori*. Planta Medica., 64: 176-178.
81. Schinazi, R.F., C.K. Chu and J.R. Babu, 1990. Anthraquinones as a new class of antiviral agents against human immuno deficiency virus. Antiviral Res., 13(5): 265-275.
82. Palani, C.S., B.T. Amala, S. Nagarajan, 1991. Antibacterlal activity of *cassia alata*. Fitoterapia, 62(3): 249-252.
83. Sydiskis, R.J., D.G. Owen, J.L. Lohr, K.H. Rosler and R.N. Blomster, 1991. Inactivation of enveloped viruses by anthraqinones extracted from plants, Antimicro. Agents. Chemother., 35(12): 2463-2466.
84. Adedayo, O., W.A. Anderson, M. Moo-Young, V. Snieckus, P.A. Patil, and D.O. Kolawole, 2001. Phytochemistry and antibacterial activity of *Senna alata* flower, Pharmaceutical biology, 39(6): 408-412.
85. Agarwal, S.K., S.S. Singh, S. Verma and S. Kumar, 2000. Antifungal activity of anthraquinones derivatives from Rheum emodi. J. Ethnopharmacol., 72(1-2): 43-46.
86. Sydiskis, R.J., J. Robert and D.G. Owen, 1987. Aloe-emodin and other anthraquinones and anthraquinone like compounds from plants virucidal against *Herpes simplex* viruses. Pat. 4670265. USA
87. Semple, S.J., S.M. Pyke, G.D. Reynolds and R.L. Flower, 2001. *In vitro* antiviral activity of the anthraquinone chrysophanic acid against poliovirus. Antiviral Res. 49(3): 169-173.
88. Zakaria, H.M., A. Sandra, J.M. Mainen and C.K. Modest, 2004. Anthranoid Compounds with Antiprotozal activity from *Vismia orientalis*. Plant Med. 70: 706-710.
89. Reichling, J., A. Weseler and R. Saller, 2001. A current review of antimicrobial activity of *Hypericum perforatum* L. Pharmaco. Psychiatry, 34(1): 116-118.
90. Avato, P., F. Raffo, G. Guglilmi, C. Vitali and A. Rosato, 2004. Extracts from St. Johns wort and their antimicrobial activity, 18(3): 230-232.
91. Lavie David, Revel Michel, Rotman Dalia, Velde Vincent. 02/06/1990. Antiviral compostion. Pat. 4898891. USA.
92. Anderson, D.O., N.D. Weber, S.G. Wood, B.G. Huyhes, B.K. Murray and J.A. North, 1991. *In vitro* virucidal activity of selected anthraquinones derivatives, 1991. Antiviral Res., 16(2): 185-196.
93. Meruelo, D., and G. Lavie, 1996. Method of treating papilloma virus infection using hypericin. A61K031 / 045, A61K031/01 Pat. 5506271, USA.
94. Lee, H.Z., S.L. Hsu and C.H. Wu, 2001. Effects and mechanisms of aloe-emodin on cell death in human lung squamous cell carcinoma. British J. Pharmacol., 431(3): 287-95.
95. Pecere, T., M. Vittoria Gazzola, C. Mucignat, C. Parolin, F.D. Vecchia, A. Cavaggioni, G. Basso, A. Diaspro, B. Salvato, M. Carli and G. Palù, 2000. Aloe-emodin is a new type of anticancer agent with slective activity against neuroectodermal tumors. Cancer Research, 60(11): 2800-4.

96. Ali, S.M. and M. Olivo, 2003. Nitric peroxide mediated photo-induced cell deth in human malignant cells. Int. J. Onocol., 22(4): 751-756.
97. Hostanska, K., J. Reichling, S. Bommer, M. Weber and R. Saller, 2003. Hyperforin a constituent of St. John's wort (*Hypericum perforatum L.)* extract induces apoptosis by triggering activation of caspases and with hypericin Synergistically exerts cytotoxcity towards human malignant cell lines. Eur. J. Pharm. Biopharm., 56(1): 121-123.
98. Dharmanda, S., 2004. The treatment of gastro - Intestinal cancers with chinese medicine. www.Itmonline org/arts/gicacer.htm Donenelly, D. and M. Sharidon, 1986. Anthraquinones from *Trichoderma polysporum*. Phytochemistry, 25: 2303-2304.
99. Tai-Lung, C., Q. Lin, C. Chun-Te, W. Yong and H. Mien-Chie, 2005. Emodin down-regulates Androgen receptor and inhibits prostate cancer cell growth. Cancer Res., 65: 2287-2299
100. Lin, S.Y., J.H. Yang, T.C. Hsia, J.H. Lee, T.H. Chiu, Y.H. Wei, and J.G. Chung, 2005. Effect of inhibition of aloe-emodin on N-acetyltransferase activity and gene expression in human malignant melanoma cells. Melanoma Res., 15(6): 489-494.