Drugs of the Future 2008, 33(8): 673-680

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.08.1220137

Review Article

Novel drug leads from Turkish medicinal plants with diverse pharmacological effects

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Abstract

Despite recent developments in computational and chemical techniques, traditional medicines are considered among the most reliable lead sources for the discovery of new drugs. A vast wealth of knowledge has been accumulated in Turkey as traditional medicinal heritage due to the rich cultural and plant diversity. Ethnopharmacological investigations have been carried out for the scientific evaluation of this information by our research team. Using *in vivo* bioassay- or *in vitro* activity-guided fractionation and isolation procedures, the active ingredients of several traditional remedies have been determined and defined chemically. In this review, several examples of the diverse pharmacological activity profile of these natural active ingredients will be discussed, *i.e.*, sesquiterpene lactones with antiulcerogenic and antiviral activities; flavonoids with antiinflammatory, antinociceptive, antiulcerogenic, anti-*Helicobacter pylori*, antidiabetic and antihepatotoxic activity; and lignans with antiinflammatory, antinociceptive and antiulcerogenic activity. The author also draws attention to the discovery of multitargeted drug molecules for rational therapy.

Introduction

Photosynthesis is one of the most important phenomena in the world and millions of molecules with diverse chemical structures are biosynthesized in lower and higher plants. These molecules have served as a source of vitality for all living beings as either food or medicine since the beginning of life on earth. It has been reported that around 300,000 higher plant species have been fully defined up to now. It is also estimated that about 200,000, or possibly more, species remain to be discovered. However, only a small fraction of these plants have been recognized as remedies in traditional medicine systems. Consequently, millions of molecules in the plant kingdom remain to be discovered as novel drug leads.

The Turkish flora are estimated to harbor more than 11,000 higher plant species. Turkey served as a bridge between Europe, Asia and Africa through the ages, and a number of different peoples settled in these lands, bringing their culture, religion and customs. Factors such as rich flora and cultural diversity have contributed to the wealth of traditional medicine in Turkey. A part of this rich ethnomedical heritage has recently been documented with extensive field surveys throughout Anatolia (Asian part of Turkey) (1).

Several research groups in Turkey have successfully carried out ethnopharmacological investigations for the scientific evaluation of this information. Using *in vivo* bioassay- or *in vitro* activity-guided fractionation procedures, several pharmacologically active molecules have been isolated and chemically defined from traditional Turkish remedies. It therefore appears that traditional Turkish medicines represent an important source of active lead structures, awaiting recognition as promising and profitable drug substances. In this review, several prominent novel drug candidates will briefly be discussed (see Table I).

Sesquiterpene lactones with antiulcerogenic and antiviral activities

The aerial parts of *Centaurea solstitialis* L. ssp. *solstitialis* (Asteraceae) [CSS] are used for the treatment of various disorders in Turkish folk medicine, including peptic ulcers, stomach upset, abdominal pain, malaria, common colds and labial herpes infections (2-4). For the evaluation of the effects of CSS on ulcerogenesis, the aqueous and methanolic extracts from the aerial parts were studied using the water immersion and immobilization-induced stress ulcer model in rats, and potent activity was found for both extracts (5). The methanolic extract and its chloroform subfraction were also shown to pos-

Table I: List of plants discussed in this review, their utilization in traditional medicine, active constituents isolated and corresponding pharmacological effects.

Latin name	Traditional use	Active ingredient	Type of constituent	Effects of active ingredient (*in vivo*; *in vitro*)
Calluna vulgaris	Rheumatic pain, gout pain, diaphoretic, cough, antiseptic, liver problems, diuretic, sedative	Kaempferol-3-*O*-β-D-galactoside	Flavonoid	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)
Centaurea solstitialis ssp. *solstitialis*	Stomach ache, abdominal pain, headache, malaria, fever, common colds, herpes infections	Chlorojanerin	Sesquiterpene lactone	Antiulcer (*in vivo*)
		13-Acetyl-solstitialin A	Sesquiterpene lactone	Antiulcer (*in vivo*), antiherpes (*in vitro*)
Cistus laurifolius	Rheumatic pain, urinary inflammation, fever, stomach ache, diabetes, alopecia	3-*O*-Methylquercetin	Flavonoid	Prostaglandin inhibition (*in vitro*), antinociceptive (*in vivo*), antiinflammatory (*in vivo*), antihepatotoxic (*in vivo*), anti-*Helicobacter pylori* (*in vitro*), antiviral (*in vitro*), platelet activation inhibition (*in vitro*), aldose reductase inhibition (*in vivo*), cAMP and cGMP inhibition (*in vitro*), antioxidant (*in vitro*)
		3,4'-Dimethylquercetin	Flavonoid	Prostaglandin inhibition (*in vitro*), antinociceptive (*in vivo*), antiinflammatory (*in vivo*), antihepatotoxic (*in vivo*)
		3,7-*O*-Dimethyl-kaempferol	Flavonoid	Antinociceptive (*in vivo*), antiinflammatory (*in vivo*), antihepatotoxic (*in vivo*)
Daphne oleoides ssp. *oleoides*	Rheumatic pain, abscess, back pain, fever, wound healing, gynecological disorders	Eudesmine	Lignan (monofuranoid)	Anti-TNF-α (*in vitro*)
		Wikstromol, matairesinol	Lignan (γ-valerolactone)	Anti-TNF-α (*in vitro*)
Gentiana olivieri	To reduce blood sugar, nervous disorders, appetite stimulant	Isoorientin	Flavonoid	Antidiabetic (*in vivo*), antihepatotoxic (*in vivo*), antiinflammatory (*in vivo*), antinociceptive (*in vivo*), antioxidant (*in vivo*), antidepressant (*in vivo*), sedative (*in vivo*), antibacterial (*in vitro*)
Geranium pratense ssp. *finitimum*	Asthma, allergies, tonic, stomach ache, diarrhea, diuretic, liver disorders, hemostatic, diabetes	Kaempferol-3-*O*-β-D-galactoside + quercetin 3-*O*-α-arabinopyranoside	Flavonoid	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)
		Quercetin 3-*O*-β-D-glucopyranoside + quercetin 3-*O*-β-D-galactopyranoside	Flavonoid	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)
Taxus baccata	Rheumatic pain, malaria, stomach ache	Baccatin VI, 1β-hydroxybaccatin I, baccatin III, taxusin	Taxoid	Antinociceptive (*in vivo*)
		3'-Demethylisolariciresinol-9'-hydroxyisopropyl ether, 3-demethylisolariciresinol	Lignan	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)
		Lariciresinol	Lignan	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*), anti-TNF-α (*in vitro*), antiulcer (*in vivo*)

Continuation

Table I (Cont.): List of plants discussed in this review, their utilization in traditional medicine, active constituents isolated and corresponding pharmacological effects.

Latin name	Traditional use	Active ingredient	Type of constituent	Effects of active ingredient (*in vivo*; *in vitro*)
Taxus baccata		Taxiresinol	Taxoid	Antinociceptive (*in vivo*), antiulcer (*in vivo*)
		Isolariciresinol	Lignan	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*), anti-TNF-α (*in vitro*), antiulcer (*in vivo*)
Tilia argentea	Common colds, cough, eczema, tooth ache, hemorrhoids, kidney pain	Kaempferol-3,7-dirhamnoside	Flavonoid	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)
		Quercetin-3,7-dirhamnoside	Flavonoid	Antiinflammatory (*in vivo*), antinociceptive (*in vivo*)

sess potent inhibitory activity against *H. pylori* strains comparable to that of reference antibiotics (6).

The alcoholic (80%) extract was then submitted to bioassay-guided procedures (BGP) for the isolation of the active constituent(s) using the ethanol (EtOH)-induced ulcerogenesis model for evaluating activity (7). Two guaianolide-type sesquiterpene lactones, chlorojanerin and 13-acetyl-solstitialin A, were isolated from the chloroform subfraction through successive column chromatographic procedures on Sephadex LH-20 and Kieselgel (Fig. 1). Despite the potent antiulcer effects of these two sesquiterpene lactones (89.6% and 89.0% inhibition, respectively), solstitialin A, a desacetyl derivative of the latter, showed only weak activity (31.2% inhibition).

Further studies were also conducted to elucidate the mechanism of action of these two sesquiterpene lactones (8). Chlorojanerin was shown to have significant efficacy in preventing the lesions induced by ethanol after both oral (p.o.) and subcutaneous (s.c.) administration, as well as in indomethacin-, indomethacin plus HCl/EtOH-, N^G-nitro-L-arginine methyl ester plus EtOH-, *N*-ethylmaleimide plus EtOH-, water immersion and restraint stress- and serotonin-induced *in vivo* ulcer models, whereas it was inactive in preventing ulcers induced by pyloric ligation, diethyldithiocarbamate and cysteamine. The other constituent, 13-acetyl-solstitialin A, showed a similar activity profile as chlorojanerin, although it was found to be effective against EtOH-induced lesions only after p.o. administration. Unlike chlorojanerin, this compound was also found to be effective against cysteamine-induced duodenal lesions.

A few sesquiterpene lactones were previously reported to be antiulcerogenic, *i.e.,* dehydroleucodine (a guaianolide) from *Artemisia douglasiana* (9) and parthenolide (a germacronolide) from *Tanacetum vulgare* (10). Giordano *et al.* (11) described several structural requirements for guaianolide and pseudoguaianolide derivatives for cytoprotective activity against EtOH-induced ulcerogenesis, *i.e.,* the presence of α,β-unsaturated cyclopentenone and α-methylene-γ-lactone moieties. According to their hypothesis, these two systems can possibly react as Michael acceptors with sulfhydryl-containing peptides of the gastric mucosa. Since the lumen of the stomach is strongly acidic, the putative Michael addition would occur in the mucosa where the pH is closer to neutral. However, due to the absence of an α,β-unsaturated cyclopentenone moiety, the structures of chlorojanerin and 13-acetyl-solstitialin A do not appear to be in accordance with this hypothesis.

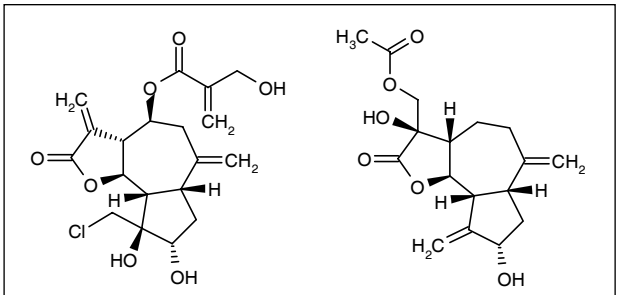


Fig. 1. Sesquiterpene lactones with antiulcerogenic activity from *Centaurea solstitialis* ssp. *solstitialis*.

13-Acetyl-solstitialin A was also shown to possess potent antiviral activity against herpes simplex virus type 1 (HSV-1), similar to that of the reference compound aciclovir (12). The aerial part of CSS has been used for the treatment of labial herpes infections in children in Turkey, and these findings support this use (3).

Phenolic plant constituents with diverse pharmacological effects

Particularly in the last two decades, increasing attention has been paid to phenolic plant constituents such as flavonoids, phenolic acids and proanthocyanins for their wide range of biological effects. Previous studies have indicated that several phenolic phytochemicals modulate arachidonic acid metabolism in platelets and peritoneal leukocytes. Similarly, a number of phenolic compounds have also been determined to be the active antiinflammatory and antinociceptive constituents of traditional remedies during bioassay-guided isolation procedures on Turkish medicinal plants, *e.g.,* the chrysoeriol derivatives

ozturkosides A to C (13), phenylethanoid glucoside and flavone derivatives of isoscutellarein glucosides (14), prenylated isoflavones (15), chalcone and flavanone derivatives (16).

A therapeutic arsenal: 3-O-methylquercetin

Rockrose (*Cistus laurifolius,* Cistaceae) leaves are used externally as a remedy for rheumatic pain, high fever and urinary inflammation in Anatolia. For this purpose, a warm decoction is used as a bath to relieve pain, or wilted leaves are applied on the affected limb (2). The decoction is also said to be useful for the treatment of cancer. In fact, the extract from leaves showed potent *in vitro* inhibitory activity against the inflammatory cytokine interleukin-1α (17). In a subsequent *in vitro* study, the extract from leaves was also found to be inhibitory against prostaglandin PGE_1- and PGE_2-induced contractions in guinea pig ileum (18). Among the 16 components from this plant with flavonoid or lignan structures obtained using *in vitro* activity-guided separation procedures, several were shown to possess inhibitory activity against prostaglandins, *i.e.*, 3-*O*-methylquercetin (MQ) (Fig. 2), 3,4'-dimethylquercetin (DMQ), quercetin 3-*O*-α-rhamnoside (RQ) and 1-(4-hydroxy-3-methoxyphenyl)-2-[4-(3-α-L-rhamnopyranosypropyl)-2-methoxyphenoxyl]-1,3-propenediol (HP). MQ, RQ and HP were also found to possess *in vitro* antioxidant activity (19).

It is well known that prostaglandins are the mediators of inflammatory reactions and that compounds affecting their receptors, such as EP_1-EP_4, may act to reduce inflammation, pain or fever. For example, PGE_2 receptors play a key role in the pathogenesis of rheumatoid arthritis (20). Chronic inflammatory conditions were also found to enhance predisposition to cancer development and it is suggested that long-term administration of nonsteroidal antiinflammatory drugs (NSAIDs) may reduce the incidence of cancer (21). Consequently, certain types of prostaglandin inhibitors are claimed to be beneficial in preventing and treating cancer (22).

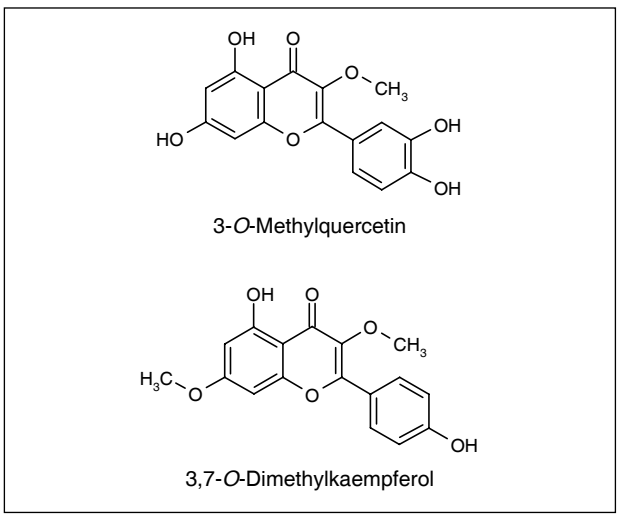


Fig. 2. Quercetin and kaempferol derivatives show potent antiinflammatory and antinociceptive effects.

Among the isolated components, MQ possessed both antiinflammatory and antioxidant effects and may be the main principle of the plant responsible for the healing effects. Several previous studies had also reported similar effects for this compound. The compound inhibited the release of histamine from peritoneal mast cells, the release of β-glucuronidase and lysozyme, and superoxide anion formation from rat neutrophils (23), and it exhibited xanthine oxidase-inhibitory and superoxide-scavenging activities (24); it also inhibited carrageenan-induced hindpaw edema and cotton pellet granuloma in mice (25).

In a recent study on the same plant by Küpeli and Yesilada (25), using *in vivo* BGP, 3,7-*O*-dimethylkaempferol (DMK) (Fig. 2) was isolated along with MQ and DMQ as the antiinflammatory and antinociceptive components, as determined in the carrageenan-induced hindpaw edema and acetic acid-induced vascular permeability models in mice. Importantly, the antiinflammatory potency of these flavonoids was found to be equal to that of indomethacin, without inducing any apparent acute toxicity or gastric damage. These compounds were also shown to possess remarkable antinociceptive effects, as evidenced by inhibitory activity against phenylbenzoquinone-induced writhing in mice. Another striking finding was that MQ, DMQ and DMK were also shown to possess potent antihepatotoxic activity against acetaminophen-induced liver damage, which might be interpreted as additional safety advantages for these compounds (26).

MQ is widely distributed in the plant kingdom and has been reported to possess several pharmacological activities. Noteworthy among these are: antiviral activity against human picornaviruses (27) and poliovirus (28), cardiovascular effects (29), inhibition of platelet aggregation (30), relaxation of *in vitro* histamine-induced tracheal constriction (31), suppressive effects on ovalbumin-induced airways hyperresponsiveness through inhibition of cAMP and cGMP phosphodiesterase (32) and inhibitory effects on aldose reductase (33). Parmer and Hennings (34) reported that MQ possesses more potent antiulcer activity than cimetidine, a well-known antiulcer agent. Since *C. laurifolius* flower buds have been used as a traditional remedy to treat peptic ulcers for over 2,000 years in Turkey, MQ may be the active ingredient of this plant (35). In fact, the plant extract was shown to possess a marked inhibitory effect on *H. pylori* strains (6) and MQ was isolated as the active anti-*Helicobacter* component, while DMQ and DMK showed weak activity (36).

Another flavonoid, kaempferol glycoside (kaempferol-3-*O*-β-D-galactoside, KGA) was isolated using BGP from the aerial parts of *Calluna vulgaris* (Ericaceae) (37). Later, during an investigation on *Geranium pratense* ssp. *finitimum* (Geraniaceae) aerial parts, a mixture of KGA with quercetin 3-*O*-β-arabinopyranoside (KGA/QA) was also shown to possess significant antiinflammatory and antinociceptive activity against carrageenan- and PGE_2-induced paw edema in mice (38). In that study, another mixture comprised of quercetin 3-*O*-β-glucopyranoside

and quercetin 3-*O*-β-galactopyranoside (QG/QGA) was shown to possess more potent activity than the KGA/QA mixture. QG and QGA were previously isolated from *Acaena magellanica* (Rosaceae) using BGP techniques as potent antiinflammatory and analgesic components (39). While the activity of kaempferol-3-*O*-β-glucopyranoside (KG) was weak, a mixture of 2"-*O*-galloyl derivatives of QG/QGA (quercetin 3-*O*-[2"-*O*-galloyl]-β-glucopyranoside and quercetin 3-[2"-*O*-galloyl]-*O*-β-galactopyranoside, QGG/QGGA) was found to be more effective in the TPA-induced ear edema model, while showing weak activity in paw edema models. These compounds were also found to be active against phenylbenzoquinone-induced writhing, indicating antinociceptive activity. Moreover, none of the active compounds caused gastric damage (38).

The main flavonoids, kaempferol-3,7-dirhamnoside (KDR) and quercetin-3,7-dirhamnoside (QDR), from the leaves of silver linden (*Tilia argentea*) have been shown to possess significant antiinflammatory and antinociceptive activity *in vivo,* supporting the traditional use of this plant (40).

Isoorientin, a C-glycosylflavone with antiinflammatory, antinociceptive and hypoglycemic activity

The flowering aerial part of *Gentiana olivieri* Griseb. (Gentianaceae) is a popular plant in eastern and southeastern parts of Turkey. Tea prepared from this plant by maceration (in cold water) is used to lower blood glucose in type 2 diabetic patients (41), while a 2-3% infusion (in hot water) is used as an appetite stimulant and antipyretic (42). For the evaluation of the blood glucose-lowering activity, aqueous and methanolic extracts were prepared and tested in normoglycemic, glucose-induced hyperglycemic and streptozotocin-induced diabetic rats. Although the water extract proved to be ineffective, the methanolic extract showed significant activity in the hyperglycemic and diabetic animals. Using bioassay-guided fractionation and isolation procedures, a flavonoid-type compound, isoorientin (Fig. 3), was isolated as the active antidiabetic component of the plant. The same compound was also found to be effective in decreasing plasma cholesterol and triglyceride concentrations upon subacute administration (43). Isoorientin also demonstrated antihepatotoxic and antioxidant activity against carbon tetrachloride-induced hepatotoxicity in rats, as assessed by monitoring biochemical parameters of plasma and/or hepatic tissue, *i.e.,* malondialdehyde (MDA) formation, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzyme levels and cellular glutathione levels, as well as histopathologically (44).

It is noteworthy that isoorientin exerted several important pharmacological activities in the experimental studies. Antiinflammatory activity, assessed using the carrageenan-induced hindpaw edema model, was more potent than that of the well-known NSAID indomethacin, while being devoid of any apparent gastric toxicity, and potent antinociceptive activity was also found against

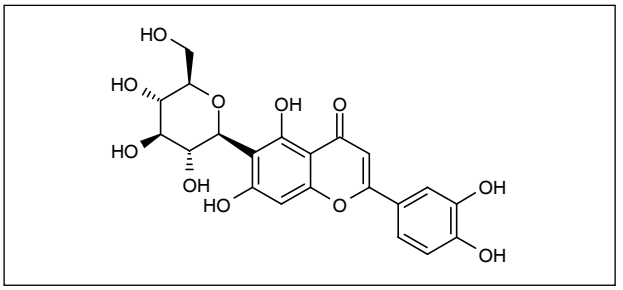


Fig. 3. A glycosylflavone, isoorientin, from the flowering herbs of *Gentiana olivieri*.

phenylbenzoquinone-induced writhing in mice (45). Isoorientin also exhibited high *in vitro* inhibitory activity against both thromboxane (TxB_2) and leukotriene (LTB_4) synthesis (46).

Isoorientin is a common C-glycosyl flavone, luteolin-6-C-β-D-glucoside, and has been reported to be found in many different plant species. This compound was also described as one of the active hypoglycemic components from the butanolic extract of a Mexican folk remedy, *Cecropia obtusifolia* (Cecropiaceae) (47). Budzianowski *et al.* (48) reported antioxidant activity evaluating the inhibitory effect on malondialdehyde (MDA) concentrations stimulated by Fe^{3+} ions and ascorbic acid in rat liver microsomes. Okuyama *et al.* reported that isoorientin, from *Jatropha cilliata*, at doses of 40 and 100 mg/kg possessed antidepressant and sedative activity as potent as that of diazepam (49). Moreover, isoorientin was shown to possess a myolytic effect on uterine smooth muscle in rats and guinea pigs, as well as antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa* (50).

Lignan derivatives with antiinflammatory, antinociceptive and antiulcerogenic effects

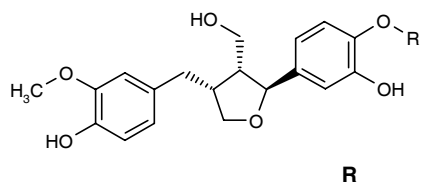
The discovery and isolation of paclitaxel from the bark of the Pacific yew *Taxus brevifolia* and its introduction in cancer chemotherapy led scientists to investigate the constituents of other *Taxus* species worldwide. The English yew *Taxus baccata* L. is a widespread plant frequently cultivated as an ornamental in gardens, although due to the toxic taxane alkaloid content it has rarely been documented as a folk remedy. In historical documents from the Roman period, this plant was recommended for use as an antimalarial and antirheumatic, while in Ayurvedic medicine it is used as an aphrodisiac, antispasmodic, sedative and emmenagogue (51), as well as for asthma (52).

In order to evaluate the antirheumatic potential of the plant, the antiinflammatory and antinociceptive activities of the extracts from the heartwood were investigated. Taxoids (27-38% inhibition at 30 mg/kg in order of decreasing potency: baccatin VI > 1β-hydroxybaccatin I > baccatin III > taxusin) and lignan derivatives (31-43% inhibition at 100 mg/kg in order of decreasing potency: lariciresinol [LR] > taxiresinol [TX] > 3'-demethylisolari-

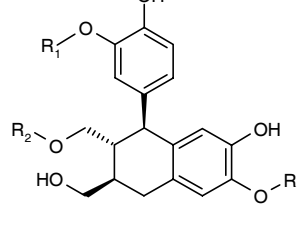
ciresinol-9'-hydroxyisopropyl ether [DIL] > 3-demethylisolariciresinol [DMI] > isolariciresinol [IL]) were isolated from the chloroform extract as the active antinociceptive constituents against phenylbenzoquinone-induced writhing, while only lignans significantly inhibited carrageenan-induced hindpaw edema in mice (53) (Fig. 4). These results were in accordance with the previous study of Cho *et al*. (54), where LR and IL were reported to possess potent *in vitro* inhibitory activity against tumor necrosis factor α (TNF-α) production. TNF-α is known to be one of the main proinflammatory cytokines secreted during the early phase of acute and chronic inflammatory diseases such as asthma, rheumatoid arthritis, septic shock, etc., and anti-TNF-α therapy is therefore expected to be beneficial (55).

In a follow-up study, the antiulcerogenic effect of the active lignans was investigated in the ethanol-induced ulcerogenesis model in rats to confirm its traditional therapeutic use. TX, IL and LR exerted marked and dose-dependent protection against gastric lesions induced by ethanol (82-85%, 58-80% and 48-77%, inhibition, respectively) at doses of 50 and 100 mg/kg, whereas the activity of DMI was weak (56). Although a wide range of biological activities, including anticancer, antibacterial, antifungal, antiviral, antioxidant and antiinflammatory effects, have been reported for lignan derivatives (57), only a few were found to possess antiulcer activity, *i.e.,* a dibenzocyclooctadiene-type lignan, isoschizandrin, from the fruits of *Schizandra chinensis* (58) and a patented lignan derivative from *Mallotus anomalus* (59).

Lignans of monofuranoid type (eudesmine) and γ-valerolactone type (wikstromol, matairesinol) were isolated from an effective remedy for rheumatic pain,



	R
1. Lariciresinol	CH_3
2. Taxiresinol	H



	R	R_1	R_2
3. Isolariciresinol	CH_3	CH_3	H
4. 3-Demethylisolariciresinol	H	CH_3	H

Fig. 4. Antiinflammatory and antinociceptive taxoids and lignan derivatives from *Taxus baccata*.

Daphne oleoides ssp. *oleoides* (Thymelaeaceae; whole plant [aerial parts plus roots]), and were also shown to possess moderate inhibitory activity on TNF-α biosynthesis (60), while inconsistent activity was observed against IL-1α and IL-1β.

Concluding remarks

Despite advances in technology, *i.e.*, combinatorial chemistry and pharmacological assay techniques, and in the understanding of biological systems, drug discovery is still a tedious process with low success rates. Futhermore, striking discrepancies have been observed in the structural and distributional characteristics of synthetic and natural molecules (61). Therefore, from the viewpoint of drug efficiency and safety, Feher and Schmidt proposed that mimicking the properties of natural molecules might be more biologically relevant (62).

Nature –plants, animals, marine organisms or microorganisms– provides a vast source for the discovery of novel bioactive molecules due to the overwhelming structural and biological diversity. This task has successfully been accomplished over the last 200 years, following the isolation of morphine alkaloid from poppy latex by Sertürner. The rational strategies for the discovery of effective lead structures from nature were well summarized in a recent paper by Rollinger and colleagues (61). It is obvious that traditional medicines are the most favorable source for achieving this goal. In fact, using *in vivo* bioassay- or *in vitro* activity-guided fractionation and isolation procedures, hundreds of active molecules in traditional medicine have been identified. Therefore, in order to increase success in drug discovery, it would be logical to pursue an integrative approach using current techniques and the experience of the past, in addition to experimental acumen.

In the current approach to therapy, strategies are generally based on treating or alleviating the symptoms identified or stated by the patients. However, this may often trigger undesired pathologies requiring further treatment. For example, NSAIDs are used for the treatment of inflammatory conditions but often cause gastric bleeding, further requiring treatment with antiulcer agents. A popular analgesic agent, acetaminophen, severely damages hepatic cells, for example, requiring additional drug treatments. In fact, these common drug toxicities are employed as *in vivo* experimental models, *e.g.,* acetaminophen-induced hepatotoxicity or indomethacin-induced ulcer, in current pharmacological investigations.

On the other hand, recent developments in bioassay-(for *in vivo*) or activity-guided (for *in vitro*) fractionation procedures have led to the isolation of phytochemicals from traditional medicines with a broad activity profile, for example, NSAIDs with antinociceptive, antiulcerogenic and antihepatotoxic activity, or molecules with antiulcerogenic effects, acting on multiple factors in peptic ulcer pathogenesis, *i.e.*, regeneration of gastric mucosa, eradication of *H. pylori* infection, reducing stress factors, as well as antisecretolytic activity. Also, certain antidiabetic

molecules have inhibitory effects on complications of diabetes, such as elevated cholesterol and triglycerides, as well as regenerating hepatic damage.

In this review, the author highlights the discovery of multitargeted drug molecules from nature with the objective of providing rational therapies with reduced adverse effects, minimizing the risk of drug intolerance. As a final word, we still have much to learn from nature.

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