Chapter

Therapeutic Role of Natural Products Containing Tannin for Treatment of Constipation

Dae Youn Hwang

Abstract

Many herbal plants and medicinal foods with laxative effects have been reported as novel therapeutic strategies for the treatment of constipation and its related diseases. Indeed, several natural products containing tannins exhibit remarkable laxative effects in a constipation model. Therefore, we reviewed the laxative effects and the mechanism of action of natural products containing tannins because tannins have a wide range of pharmacological activities against human diseases. These products improved the excretion parameters, histological structure, mucin secretion and the downstream signaling pathway of muscarinic acetylcholine receptors (mAChRs) in the constipation model. This review provides strong evidence that various medicinal plants containing tannins are important candidates for improving chronic constipation.

Keywords: laxative effects, tannin, natural products, excretion parameters, constipation

1. Introduction

Chronic constipation is a complex gastrointestinal disease that is characterized by infrequent bowel movements, difficult defecation, sensation of incomplete bowel evacuation, sensation of anorectal obstruction, and the need for excessive straining [1–3]. This disease can be roughly classified into three groups: (i) constipation in the elderly and cancer patients; (ii) constipation related to neuromuscular diseases and (iii) functional constipation [1]. Constipation can be caused by a variety of factors including insufficient dietary fiber or fluid intake, decreased physical activity, drug administration, colorectal cancer obstruction, and hypothyroidism [4].

Meanwhile, the most common types of drugs used to treat patients with chronic constipation can be classified into bulk laxatives, osmotic laxatives, emollient laxatives, and prokinetic and prosecretory agents [1, 5, 6]. Among these, stimulant laxatives such as bisacodyl and natrium picosulfate are commonly administered to chronic patients although they have some limitations including high costs and undesirable side effects [7]. These laxatives significantly enhance the motility and secretion of the intestine by regulating electrolyte transport by the intestinal mucosa [8]. Many bulking agents and osmotic laxatives successfully treat constipation in elderly and cancer patients and in neuromuscular diseases, while prokinetic and prosecretory agents are prescribed to patients with functional constipation (**Table 1**) [9].

Drug class	Generic name	Comments	Dose
Bulking agents	Psyllium Ispaghula	Effective Effective	25–30 g daily in divided doses 3.5 g to three times daily
Osmotic laxative	Polyethylene glycol	Effective Unpalatable taste	17 g in 237 ml solution daily
	Lactulose	Effective May causes bloating, flatulence and cramping	13–30 ml (667 mg/ml) daily
Stimulant laxatives	Bisacodyl	Effective, but the effects subside with time, can cause cramping	5–20 mg daily
	Natrium picosulfate		5–10 mg daily
Emollient laxative	Mineral oil	Effective	5–10 cm^3 daily
	Glycerin suppositories	Effective Initiates evacuation by distending the rectum	On demand
Prokinetic and prosecretory agents	Prucalopride	Effective. May cause headache, nausea, abdominal pain and diarrhea. These adverse events occur within the first 24 h of treatment and are short lived	2 mg daily
	Linaclotide	Diarrhea is the most common side effect	290 μg daily

Table 1.
Classification of drugs used to treat patients with chronic constipation [1].

To date, the laxative activities of natural products containing various bioactive compounds have been investigated in terms of the regulation of intestinal motility, ileum tension, frequency of defecation, and number of stools. Leaf extracts of *Aloe ferox* Mill., agarwood (*Aquilaria sinensis*, *A. crasna*), and common fig (*Ficus carica*) paste are reported to significantly increase the total stool weight and intestinal motility and to normalize body weight in constipated rats treated with loperamide (Lop) [10–12]. The water extract of Cactus (*Opuntia humifusa*) successfully improves the stool number and water content, as well as the histological parameters of the intestine [13]. High laxative activity and improvement of constipation symptoms were also observed after treatment with *Mareya micrantha* (Benth.) Mull. Arg. (Euphorbiaceae) in the Lop-induced constipation model [14]. A laxative effect compared to the standard drug (bisacodyl) was also detected with the methanol and hexane extracts of *Senna macranthera* leaves [15]. Furthermore, an aqueous extract of *Liriope platyphylla* recovered the frequency and weight of stools, villus length, crypt layer thickness, muscle thickness, mucin secretion, and accumulation of lipid droplets in crypt enterocytes [16]. The laxative effects of *L. platyphylla* correlated with the signaling pathway of mAChRs [16]. Although the laxative activity of many natural products has been reported, a relationship between natural products containing tannin and laxative effects has never been focused until now.

In the present review, we focused on the laxative effects and mechanism of action of natural products containing tannin in a constipation model. This study is the first to

suggest that natural products containing tannin may be as effective at alleviating constipation as commercial drugs such as bisacodyl, sennoside calcium, and docusate sodium.

2. Laxative effects and mechanism of action of natural products containing tannin

2.1 Role of tannin as health-benefiting biomolecules

Tannins are the most abundant secondary metabolites in plants and are well known as one of the major groups of antioxidants polyphenols. These compounds are found in various foods and beverages including coffee, tea, wine, grapes, blueberries, pomegranate, and strawberries [17]. They are abundantly distributed in leaves, wood, tree bark, fruit, and roots. Indeed, tannin accounts for 5–10% of the dry weight of plant leaves (**Table 2**) [18].

Tannins have been classified into three major groups: hydrolysable tannin (HT), phlorotannins (PT), and condensed tannin (CT). HTs are compounds with polyol (D-glucose) esterified by phenolic groups and include gallic acid and ellagic acid [19]. CTs are oligomers or polymers of polyhydroxy flavan-3-ol unit (polyphenolic bioflavonoids) and include catechin and epicatechin. HTs are usually distributed in low amounts in plants, while CTs are abundantly or widely distributed in plants (**Table 2**) [20].

Tannins have a wide range of biological and pharmacological activities including antioxidative, anticarcinogenic, anti-inflammatory, antibacterial, cardioprotective and anti-mutagenic activities [17]. Tannin also decreases the blood glucose level in diabetic rats and inhibits adipogenesis in adipose cells [21, 22]. These therapeutic effects are thought to be attributed to the ability of tannins to act as free radical scavengers and to activate antioxidant enzymes, although further studies are needed to confirm this [17]. Because of the versatility of tannins, novel functions of tannins in various chronic diseases have received a great deal of attention because they have great economy and potential ability as therapeutic drugs.

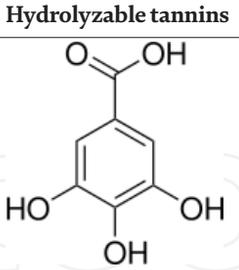
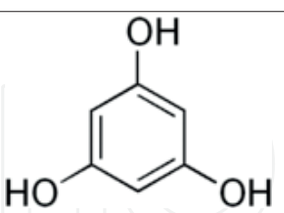
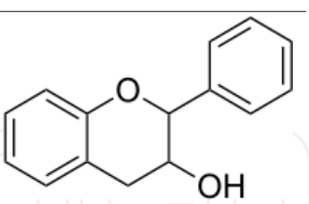
Category	Hydrolyzable tannins	Phlorotannins	Condensed tannins
Structure of basic unit			
Name of basic unit	Gallic acid	Phloroglucinol	Flavan-3-ol's scaffold
Sources	Pomegranate, strawberries, raspberries, clove, barley, oat, rye, etc.	Brown algae	Coffee, tea, wine, grapes, cranberries, apples, rosemary, etc.
Major compounds	Gallotannins, ellagitannins, punicalagin, ellagic acid, hexahydroxydiphenic acid	Diphlorethol, trifuhalol A, difucophlorethol A, dieckol	Catechin, epicatechin, gallocatechin, epigallocatechin, luteolin, quercetin, arbutin, vanillic acid

Table 2.
Three classifications of tannin [23].

2.2 Laxative effects of natural products containing tannin

2.2.1 Laxative effect of Mareya micrantha Mull. Arg

M. micrantha is a shrub tree that grows in west and central regions of Africa. The leaves of this plant have been used traditionally to treat several diseases including tapeworm infections, gonorrhea, leprosy, and constipation [24, 25]. However, scientific evidence for the therapeutic effects of this plant in several chronic diseases has also been reported. The aqueous extracts of *M. micrantha's* leaf inhibited cardiac contractibility in the hearts of frogs and rats [26, 27], but induced contraction of longitudinal muscle in the guinea pig [28]. The methanol, aqueous, and ethanol extracts of leaves also showed anti-bacterial effects against some pathogens and antiplasmodial activity against *Plasmodium falciparum* [25, 29]. Also, these aqueous leaf extracts of *M. micrantha* had 566.66 kg/body weight of LD_{50} and were classified as low toxic substance [30]. Meanwhile, the aqueous leaf extract of *M. micrantha* contained various phytochemicals including alkaloids, tannins, flavonoids, polyphenols, sterols and polyterpenes although their concentrations were low [31].

Furthermore, the aqueous leaf extract of *M. micrantha* enhanced the gastrointestinal motility, intestinal water secretion, intestinal ion secretion, and stool output in a dose-dependent manner (100, 200 and 400 mg/kg) in Wistar rats. Similar effects were observed in The loperamode (Lop)-induced constipation model. The total stool number and weight were significantly increased after treatment with the aqueous leaf extract of *M. micrantha* (**Table 3**). The laxative effects of this product at 400 mg/kg were very similar to those of 5 mg/kg of sodium picosulfate [31].

2.2.2 Laxative effects of A. ferox Mill

A. ferox is an arborescent perennial shrub that is widely distributed in Southern Cape, Eastern Cape, Southern parts of KwaZulu Natal, the Free State and Lesotho [10]. This plant has been widely used in traditional medicine because of its healing properties against several human diseases [32], particularly tooth abscesses [33], sexually transmitted infections [34], wound healing [35], arthritis and rheumatism [36], conjunctivitis and eye ailments [37] and as an insect repellant [38].

The acetone extract of the whole leaf of *A. ferox Mill*. contained phenols (70.33%), flavonols (35.2%), proanthocyanidins (171.06%) and alkaloids (60.9%), while the ethanol extract contained the same compounds at values of 70.24%, 12.53%, 76.7% and 23.76%, respectively. Their concentrations in aqueous extract were lower than those in acetone and ethanol. In contrast, tannin levels were consistently 0.014–0.027% in all the solvent extracts [39].

Treatment	Dose	Weight of feces (g)
Control	5 mL/kg	0.938 ± 0.45
Sodium picosulfate	5 mg/kg	3.84 ± 0.62**
MAR	100 mg/kg	2.602 ± 0.33
MAR	200 mg/kg	2.806 ± 0.42*
MAR	400 mg/kg	3.507 ± 0.45**

Values are expressed as mean ± S.E.M (n = 5).
**p < 0.05 compared to control group.*
***p < 0.01 compared to control group.*

Table 3.
Laxative effect of M. micrantha aqueous extract (MAR) on Lop-induced constipation model [30].

Although various effects of this plant have been reported previously, scientific evidence for laxative effects of *Aloe ferox* was reported recently. The aqueous extract of *A. ferox* remarkably enhanced the water intake and the number, water content and weight of stools in the Lop-induced constipation model (**Table 4**). Also, a significant increase in the gastrointestinal transit ratio was induced by the administration of aqueous extract of *A. ferox*. These effects of this plant at 200 mg/kg were comparable to those of senokot [10]. Moreover, this extract was not induced any significant toxic effect on the hematological parameters for kidney and the liver function at 50, 100 and 200 mg/kg body weight for 7 days [40].

2.3 Laxative effects of *Urginea indica* Kunth

U. indica belongs to family Liliaceae and is distributed in western Himalayas and Coromandel Coast [41]. This plant was traditionally used to treat skin diseases, asthma, cough, bronchitis, calculous affections, rheumatism, leprosy, paralytic affection, internal pain, and scabies [42–44]. The bulbs of this plant were applied to relieve constipation and indigestion, to prevent burning sensations, and to remove corns and warts [41, 44, 45]. Also, its antifungal, antiangiogenic and pro-apoptotic effects were reported previously [46, 47]. Various phytochemical components including alkaloids, tannins and coumarins were detected in the crude aqueous-methanol extract of *U. indica* [48].

Laxative effects of *U. indica* have been examined in rabbits, guinea pigs and mice. The charcoal meal transit was accelerated in the small intestine of mice treated with *U. indica*. The total number of stools also increased in a dose-dependent manner in *U. indica*-treated mice. Furthermore, concentration-dependent spasmogenic effects of crude extract of *U. indica* were detected in guinea-pig ileum and rabbit jejunum (**Figure 1**) [48]. Moreover, this study provided the first evidence that the stimulant effect of *U. indica* was mediated by the activation of muscarinic receptors initiating the prokinetic effect [48].

Parameters	Normal control	Constipated control	Constipated + *A. ferox* (mg/kg body weight)			Senokot
			50	100	200	
Feed intake	17.18 ± 1.36^{a}	19.23 ± 3.86^{a}	19.90 ± 1.61^{a}	20.54 ± 1.38^{a}	17.80 ± 1.60^{a}	19.97 ± 3.31^{a}
Water intake	19.62 ± 2.22^{a}	11.72 ± 2.47^{b}	16.57 ± 2.05^{a}	17.24 ± 0.17^{a}	19.79 ± 2.33^{a}	18.14 ± 0.61^{a}
Number of fecal pellet	73.57 ± 4.39^{a}	38.20 ± 2.21^{b}	45.43 ± 1.90^{c}	57.57 ± 1.62^{d}	69.83 ± 4.49^{a}	63.00 ± 3.11^{a}
Water content of fecal pellet (ml)	14.40 ± 0.08^{a}	1.04 ± 0.09^{b}	1.75 ± 0.21^{c}	1.95 ± 0.11^{c}	2.25 ± 0.21^{d}	2.09 ± 0.06^{d}
Weight of fecal pellet (g)	7.14 ± 0.23^{a}	3.34 ± 0.38^{b}	5.72 ± 0.18^{c}	7.42 ± 0.33^{a}	8.10 ± 0.72^{a}	7.31 ± 0.25^{a}
Body weight gain (g)	15.30 ± 1.00^{a}	33.80 ± 1.00^{b}	14.20 ± 0.71^{a}	13.20 ± 2.16^{a}	12.50 ± 1.85^{a}	15.35 ± 1.21^{a}

Data are mean ± SD values (n = 4). Row values with different superscripts than the control are significantly different (P < 0.05).

Table 4.
Laxative effect of aqueous extract of A. ferox in constipated rats [31].

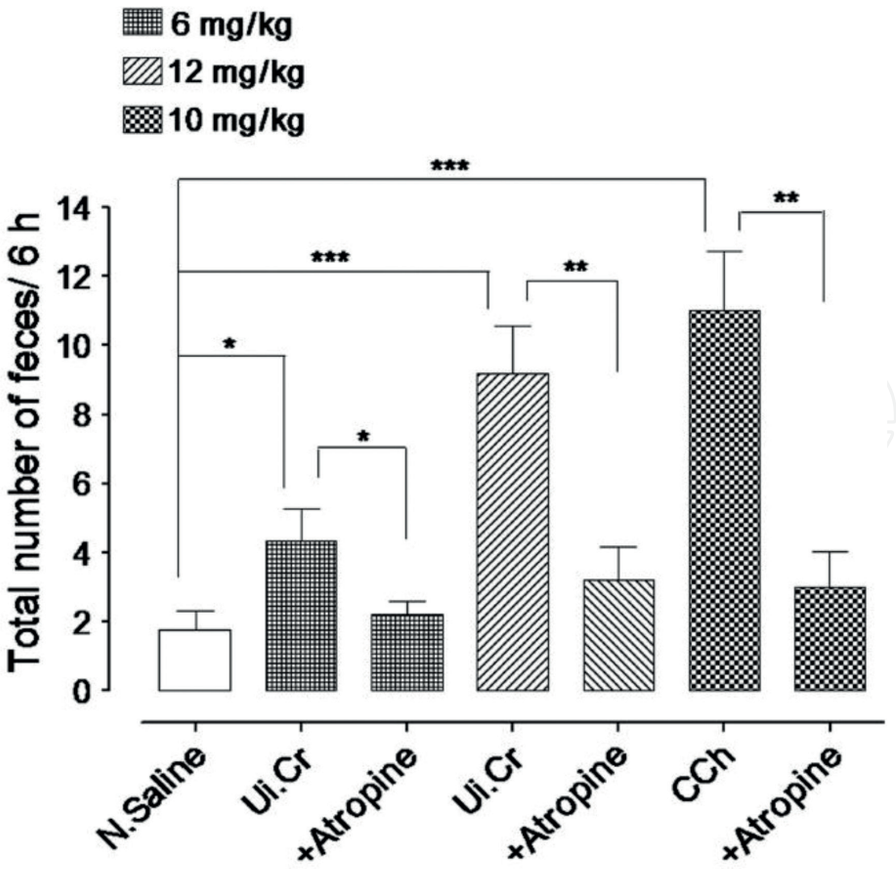


Figure 1.
*Effect of U. indica crude extract (Ui.Cr) and carbachol (CCh) on fecal number in the presence and absence of atropine. Values are expressed as mean ± SEM, n = 6. *p < 0.05 compared to control, **p < 0.01 compared to control and ***p < 0.001 compared to control [47]. Abbreviations: N. Saline, normal saline; +atropine, atropine cotreatment.*

2.4 Laxative effects of *Fumaria parviflora*

F. parviflora is an annual flowering plant and is widely distributed in many parts of the world including the Middle East and South Asia [43, 49]. The aqueous-methanol extract of this plant contained alkaloids such as adlumidiceine, coptisine, fumariline, parfumine, protopine [50], fumaranine, fumaritine, paprafumicin, paprarine [51], fumarophycine, cryptopine, sanactine, stylopine, bicuculline, adlumine, perfumidine and dihydrosanguirine [52]. Also, the aqueous-methanol extract of *F. parviflora* contained alkaloid, saponins, anthraquinones and tannins [53].

In Greco-Arab traditional medicine, this plant was used to treat indigestion, constipation, abdominal cramps and diarrhea [43, 49]. Recently, the laxative and prokinetic activity of this plant were investigated in three different animals. The charcoal meal GI transit, defecation and number of wet stools were enhanced in a dose-dependent manner in mice. Also, this plant induced a concentration-dependent, atropine-sensitive stimulatory effect both in mouse tissues (jejunum and ileum) and rabbit jejunum (**Figure 2**) [14].

2.5 Laxative effects of *Phyllanthus emblica*

P. emblica is a natural plant distributed in most areas of the Sind and Punjab provinces of Pakistan [43]. Most parts of this plant including the fruit, seed, leaves, root, bark and flowers are used in the herbal preparations due to their high phenolic contents [54].

The leaves of *P. emblica* contain tannins like glucogallin, corilagin, chebulagic acid, tannins emblicanins A and B [55], and apigenin glucoside [56]. The roots of this plant

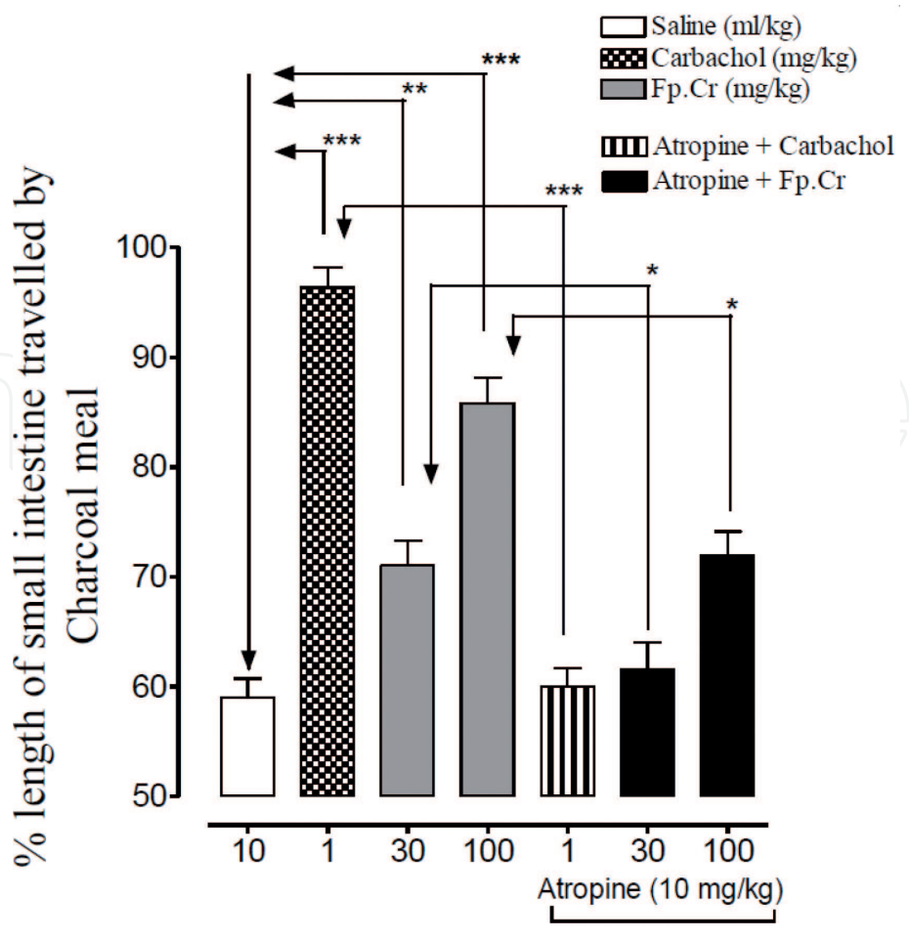


Figure 2.
*Laxative effects of F. parviflora (Fp.Cr) crude extract on travel of charcoal meal through small intestine of mice, in the absence and presence of atropine. *p < 0.05 compared with control, **p < 0.01 compared to control and ***p < 0.001 compared to control [52].*

contain norsesquiterpenoid glycosides (4′-hydroxyphyllaemblicin B, phyllaemblicins E and F, phyllaemblic acid, phyllaemblicin A, B and C) [57], quercetin and b-sitosterol [58]. The leaves are known to have multiple health benefits including gastroprotective, anti-ulcerogenic, hypolipidemic and antidiabetic [59], antioxidant [60], hepatoprotective [61], antihypertensive [62], anti-inflammatory [63], antidiarrheal and antispasmodic [64] activities. But, the crude extract of dried fruits showed laxative effects that increased charcoal meal GI transit, the mean weight of defecation, and the number of stools. The crude extracts and aqueous fraction induced dose-dependent and partially atropine-sensitive contraction in isolated guinea-pig ileum and rabbit jejunum, while the petroleum fraction showed full atropine-sensitive contraction. In contrast, spasmolytic activity was detected in the ethylacetate and chloroform fractions of this plant (**Figure 3**) [54]. Furthermore, extracts from the leaves of *P. emblica* showed 9.911 g/kg of LD50 and the indexes of thymus and spleen in the *P. emblica* extract–treated groups had no markedly difference [65].

2.6 Laxative effects of Galla Rhois

The laxative effect of Galla Rhois as a natural product containing high concentrations of tannin was investigated by Kim et al. [66]. Galla Rhois is an excrescence formed by parasitic aphids, primarily *Schlechtendalia chinensis Bell*, on the leaf of sumac, *Rhus javanica* (Anacardiaceae) (**Figure 4**) [67]. This product has been widely used for treatment of various diseases including diarrhea, seminal emissions, excessive sweating, boil, some skin diseases, bleeding, and chronic cough because of its

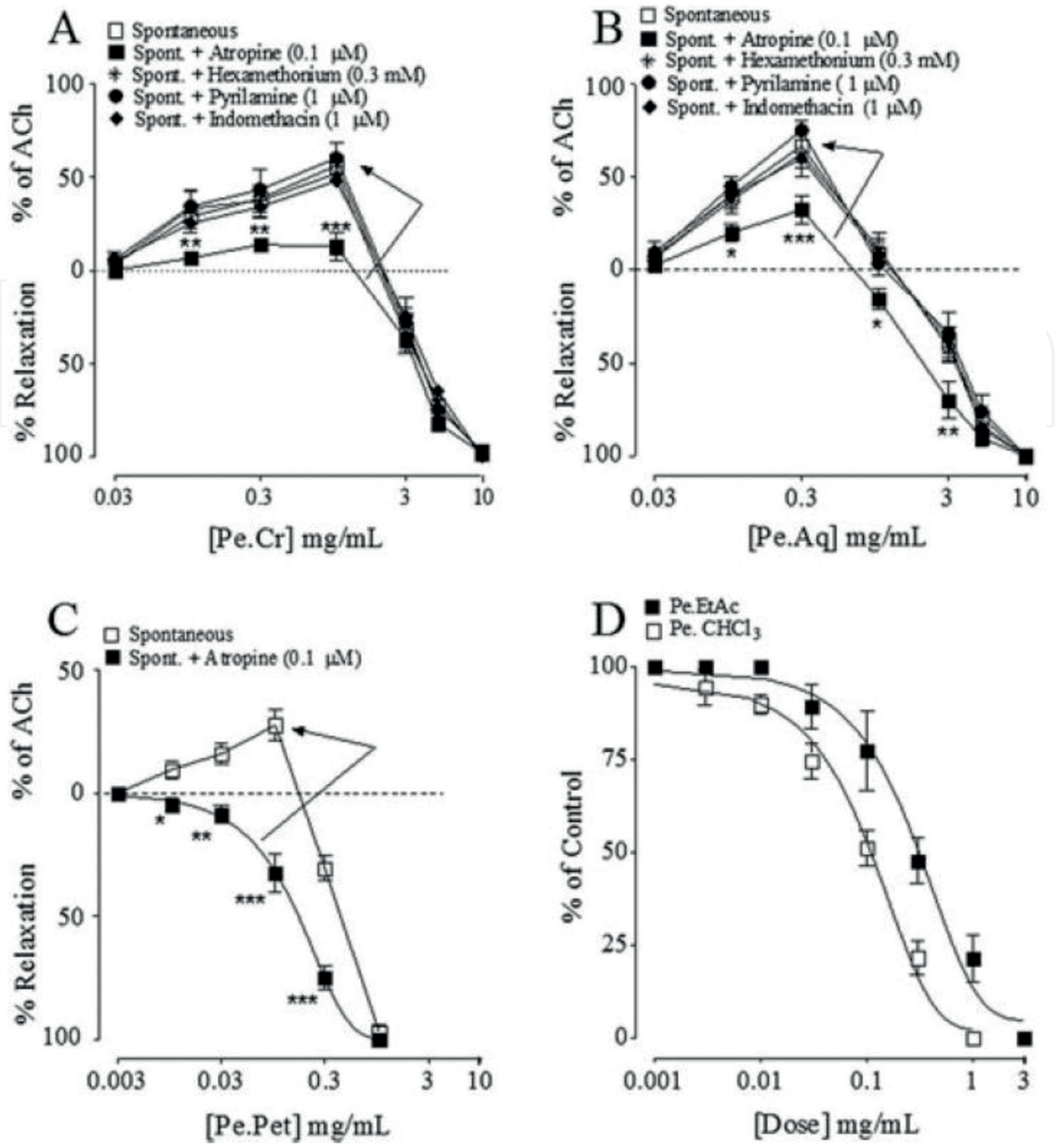


Figure 3.
*Stimulant and relaxant effects of several extracts and fractions of P. emblica. The concentration of acetylcholine (Ach) was measured in rabbit jejunum after treatment with (A) the crude extract (Pe.Cr), (B) the aqueous extract (Pe.Aq) in the absence and presence of atropine, hexamethonium, pyrilamine and indomethacin, (C) the effect of petroleum fraction (Pe.Pet) in the absence and presence of atropine, (D) the ethyl acetate (Pe.EtAc) and chloroform (Pe.CHCl$_3$) fractions. Values shown represent mean ± SEM of 6–7 determinations. *p < 0.05 compared with control, **p < 0.01 compared with control, and ***p < 0.001 compared with control [54]. Abbreviations: Spont., spontaneous.*

Figure 4.
Living and dry forms of Galla Rhois [76].

ethnopharmacological properties [67–69]. In particular, the antibacterial effects of Galla Rhois have been detected against many pathogenic bacteria such as *Salmonella* spp., *Escherichia coli* and *Eimeria tenella* [70–72], while anti-inflammatory activity is observed in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages [73]. Also, Galla Rhois shows anticancer activity against nasopharyngeal carcinoma cells [74] and improves sensorimotor function in a cerebral ischemia rat model [75].

Meanwhile, the ingredients in gallotannin-enriched Galla Rhois (GEGR) have been measured by UV-Vis spectra and HPLC analyses. They consist of gallotannin (69.2%), gallic acid (26.6%) and methyl gallate (4.2%) (**Figure 5**) [66].

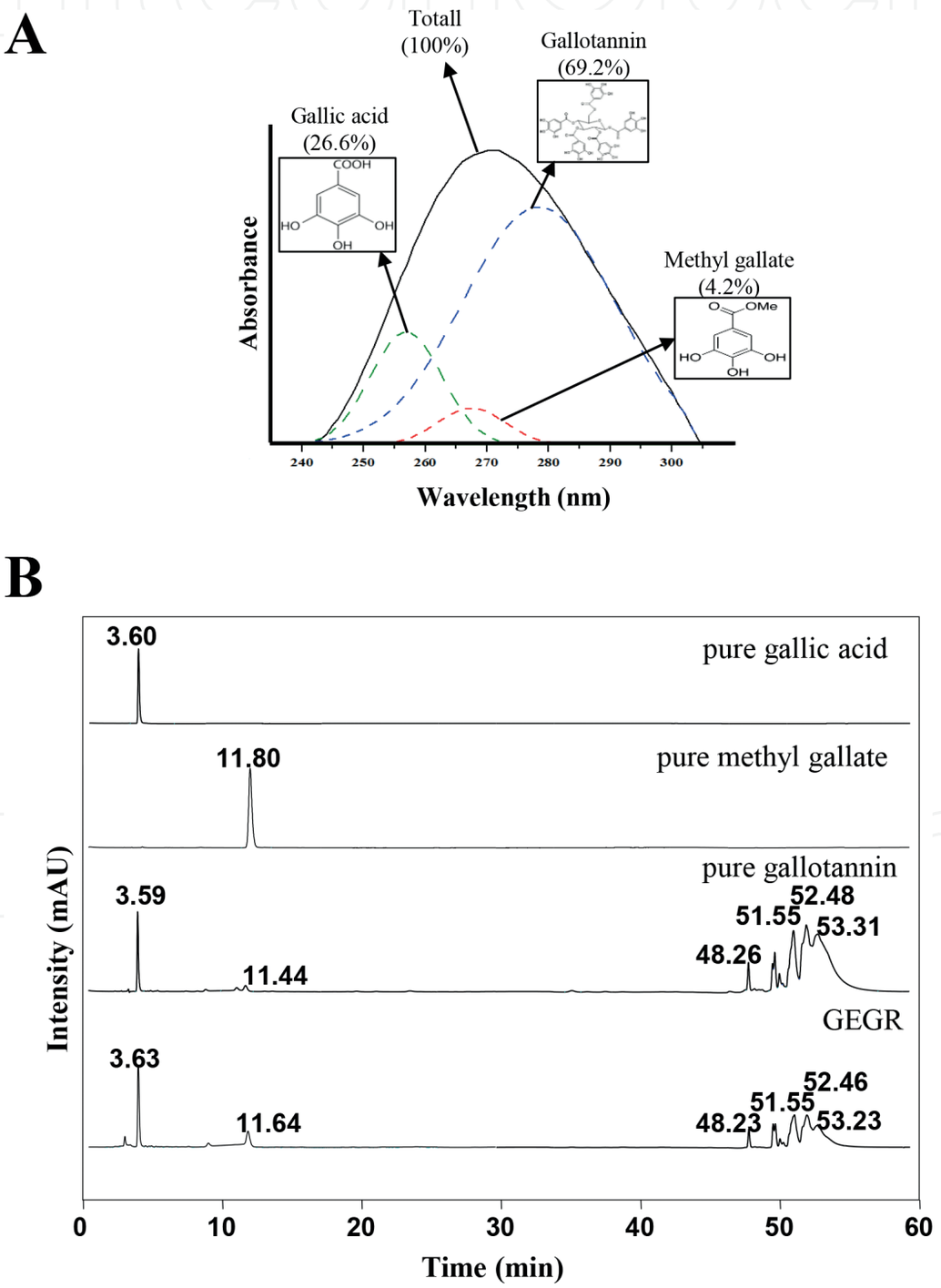


Figure 5.
Ingredients of GEGR. Concentration of major components. (A) The levels of gallotannin, gallic acid and methyl gallate in GEGR were analyzed based on their UV-vis spectra. (B) HPLC chromatograms of pure gallic acid (commercial chemical), pure methyl gallate (commercial chemical), pure gallotannin (commercial chemical), and GEGR extract [66].

In the Lop-induced constipation model, the number and weight of stools was almost recovered in the GEGR-treated groups compared to those in the untreated and vehicle-treated groups. Also, significant alterations in the thickness of the

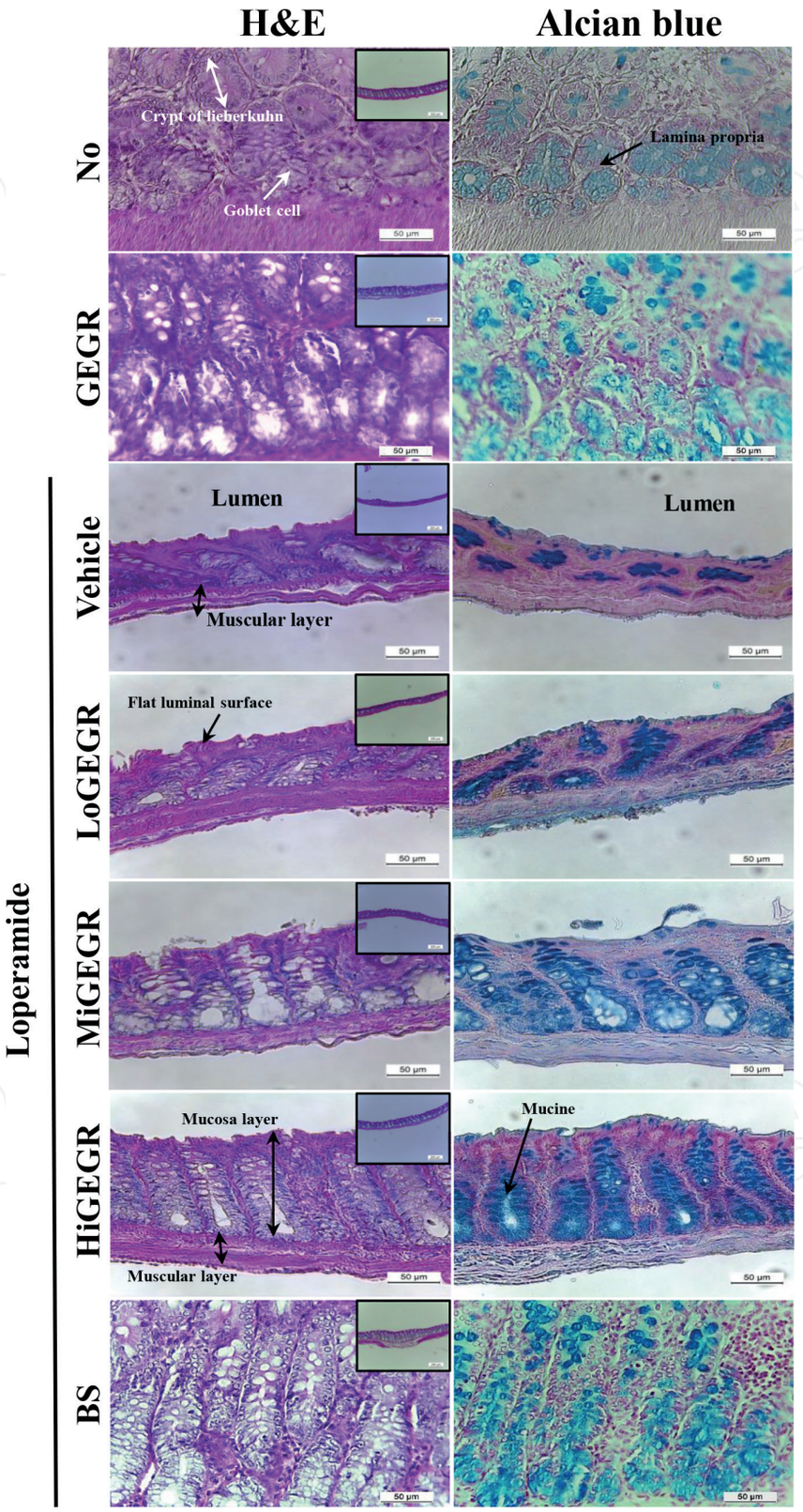


Figure 6.
Recovery effects of GEGR on the histological structure of transverse colon. After collecting the transverse colon from the subset group, these tissues were stained with H&E solution and Alcian blue. Their morphological features were observed at 100X (upper corner in left column) and 200x (left column and right column) using a light microscope [66]. Abbreviations: No, no treated group; BS, bisacodyl-treated group; LoGEGR, low level of GEGR-treated group; MiGEGR, medium level of GEGR-treated group; HiGEGR, high level of GEGR-treated group.

mucosa, muscle, and flat luminal surface, as well as in the ability to secrete mucin, were detected in the transverse colon of constipated SD rats (**Figure 6**) [66].

Furthermore, the mechanism of GEGR action during the laxative effects was investigated on the downstream signaling pathway of the muscarinic acetylcholine receptor. The Lop + GEGR-treated group was remarkably recovered compared to the Lop + vehicle-treated group. A similar pattern was detected for the phosphorylation levels of protein kinase C (PKC) and phosphoinositide 3-kinase (PI3K), the levels of Gα expression and the inositol triphosphate (IP3) concentration after GEGR treatment (**Figure 7**) [66]. However, GEGR did not induce any significant toxic effect on liver and kidney organs of ICR at doses of 1000 mg/kg body weight/day [69].

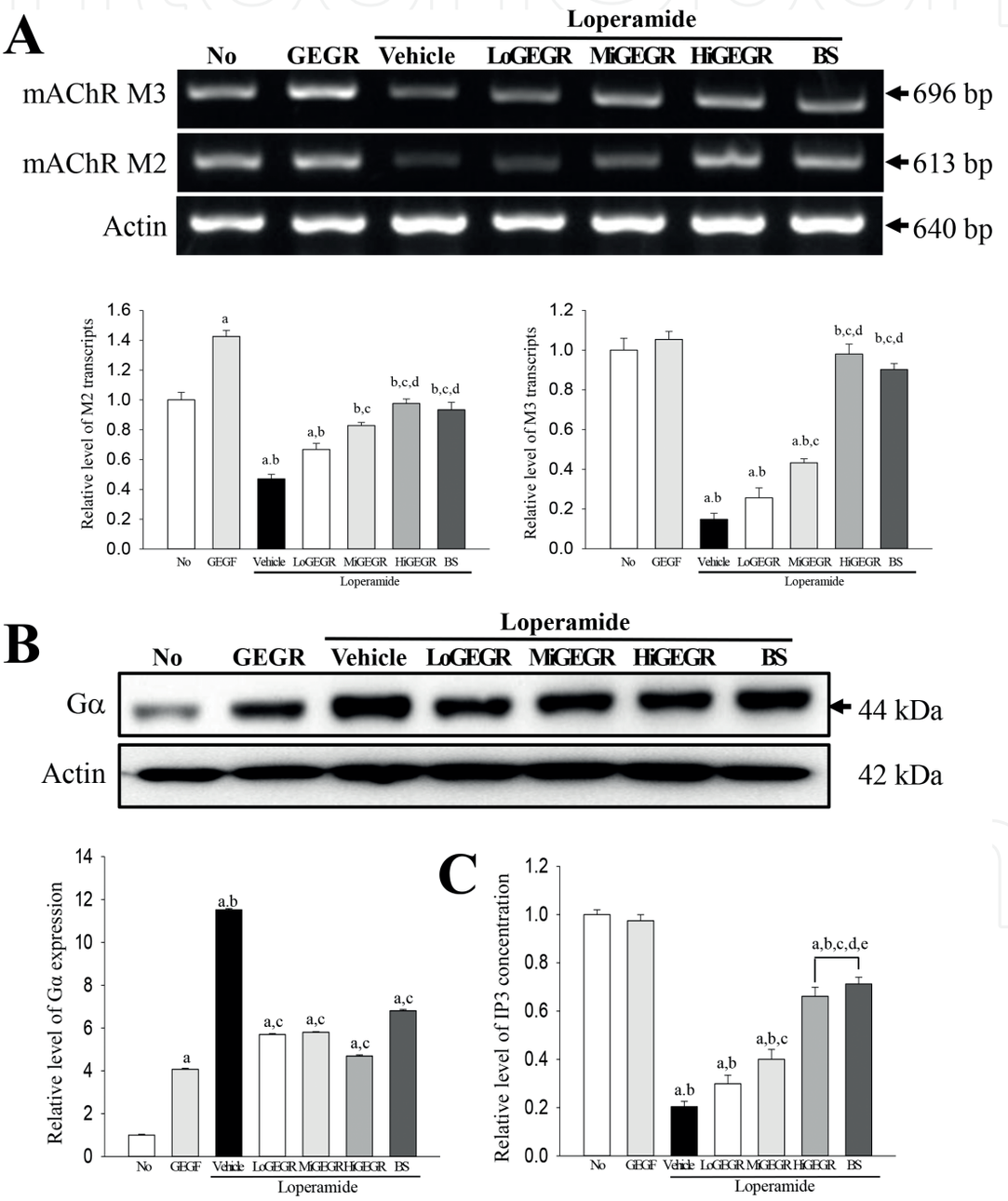


Figure 7.
Recovery effects of GEGR and mAChRs transcript and their downstream effectors. (A) The levels of mAChR M2 and M3 transcripts were measured by RT-PCR using specific primers. (B) The expression of Gα was measured by Western blotting using HRP-labeled anti-rabbit IgG antibody. (C) The IP3 concentration in total tissue homogenates was quantified by enzyme-linked immunosorbent assay. The relative levels of protein and transcript of mAChRs were calculated based on the intensity of actin protein and mRNA [66]. Abbreviations: No, no treated group; BS, bisacodyl-treated group; LoGEGR, low level of GEGR-treated group; MiGEGR, medium level of GEGR-treated group; HiGEGR, high level of GEGR-treated group; mAChR, muscarinic acetylcholine receptor.

3. Conclusions

Various bioactive molecules with therapeutic effects on human diseases have been isolated from many traditional plants including medicinal plants, aromatic plants, vegetables, and fruits [77]. Among these, tannins are some of the many

Name of natural products	Constituents	Laxative effects	Reference
M. micrantha (Benth.) Mull. Arg.	Alkaloids, tannins, flavonoid, polyphenols, sterols and polyterpenes	- Increase the gastrointestinal motility - Increase the intestinal water secretion - Increase the intestinal ion secretion - Increase the stools parameters	[31]
A. ferox Mill.	Phenols, flavonoid, proanthocyanidins, alkaloids and tannins	- Increase the stools parameters - Increase the gastrointestinal transit ratio	[10]
U. indica Kunth.	Alkaloids, tannins and coumarins	- Increase the gastrointestinal transit ratio - Increase the stools parameters - Show the concentration-dependent spasmogenic effects	[48]
F. parviflora	Alkaloids, saponins, anthraquinones and tannins	- Increase the gastrointestinal transit ratio - Increase the stools parameters - Show the concentration-dependent spasmogenic effects	[52]
S. macranthera	Flavonoids, tannins and coumarins	- Increase the gastrointestinal motility - Increase the stools parameters	[15]
P. emblica	Alkaloids, saponins, tannins, terpenes, flavonoid, sterol and coumarins	- Increase the gastrointestinal transit ratio - Increase the stools parameters - Show the concentration-dependent spasmogenic effects	[54]
Galla Rhois	Gallic acid, methyl gallate and gallotannin	- Increase the stools parameters - Recovery the histopathological structure - Increase the mucin secretion ability - Recovery the mAChRs downstream signaling pathway	[66]

Table 5.
Summary of natural products containing tannin and their laxative effects.

phytochemicals and have various pharmacological activities against many chronic diseases such as cardiovascular disease, inflammatory diseases, cancer, obesity and diabetes due to their high antioxidant activity [17]. Tannins have also received a great deal of attention as novel therapeutic drugs for use in the treatment of chronic constipation and its related conditions. In an effort to identify candidate drugs for the treatment of chronic constipation and verify the role of tannins as key laxatives, this review describes some of the evidence supporting the use of natural products containing tannin as laxatives in several constipation models. Excellent laxative effects were detected for extracts of *M. micrantha*, *A. ferox*, *U. indica*, *F. parviflora*, *S. macranthera* and *P. emblica*. In particular, Galla Rhois, which contains a high concentration of gallotannin (69.2%), remarkably improved the symptoms of constipation (**Table 5**).

In conclusion, this review provides evidence correlating the laxative effects with natural products containing tannin, although the mechanism of action has not been completely verified. Therefore, tannins may be a viable laxative treatment of humans. However, more research is needed to verify the molecular mechanism and long-term effects of each tannin type.

Acknowledgements

I would like to express my gratitude to my students, including JE Kim, ML Lee, JJ Park, BR Song, HR Kim, JW Park, MJ Kang, HJ Choi and SJ Bae, for helping to compile this paper and for helping with the graphics and charts herein. This review was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A3B03032631).

Author details

Dae Youn Hwang
Department of Biomaterials Science, College of Natural Resources and Life Science, Pusan National University, Miryang, Korea

*Address all correspondence to: dyhwang@pusan.ac.kr

References

[1] El-Salhy M, Svensen R, Hatlebakk JG, Gilja OH, Hausken T. Chronic constipation and treatment options (review). Molecular Medicine Reports. 2014;**9**(1):3-8

[2] Walia R, Mahajan L, Steffen R. Recent advances in chronic constipation. Current Opinion in Pediatrics. 2009;**21**:661-666. DOI: 10.1097/MOP.0b013e32832ff241

[3] Emmanuel AV, Tack J, Quigley EM, Talley NJ. Pharmacological management of constipation. Neurogastroenterology and Motility. 2009;**21**:41-54. DOI: 10.1111/j.1365-2982.2009.01403.x

[4] Leung FW. Etiologic factors of chronic constipation: Review of the scientific evidence. Digestive Diseases and Sciences. 2007;**52**:313-316. DOI: 10.1007/s10620-006-9298-7

[5] Liu LWC. Chronic constipation: Current treatment options. Canadian Journal of Gastroenterology. 2011;**25**(suppl B):22B-28B

[6] Hussain ZH, Everhart K, Lacy BE. Treatment of chronic constipation: Prescription medications and surgical therapies. Gastroenterology & Hepatology. 2015;**11**(2):104-114

[7] Tzavella K, Riepl RL, Klauser AG, Voderholzer WA, Schindbeck NE, Müller-Lissner SA. Decreased substance P levels in rectal biopsies from patients with slow transit constipation. European Journal of Gastroenterology & Hepatology. 1996;**8**:1207-1211

[8] Schiller LR. The therapy of constipation. Alimentary Pharmacology & Therapeutics. 2001;**15**:749-763. DOI: 10.1046/j.1365-2036.2001.00982.x

[9] Quigley EM, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: The efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—A 12-week, randomized, double-blind, placebo-controlled study. Alimentary Pharmacology & Therapeutics. 2009;**29**:315-328. DOI: 10.1111/j.1365-2036.2008.03884.x

[10] Wintola OA, Sunmonu TO, Afolayan AJ. The effect of *Aloe ferox* Mill. in the treatment of loperamide-induced constipation in Wistar rats. BMC Gastroenterology. 2010;**10**:95-99. DOI: 10.1186/1471-230X-10-95

[11] Kakino M, Izuta H, Ito T, Tsuruma K, Araki Y, Shimazawa M, et al. Agarwood induced laxative effects via acetylcholine receptors on loperamide-induced constipation in mice. Bioscience, Biotechnology, and Biochemistry. 2010;**74**:1550-1555. DOI: 10.1271/bbb.100122

[12] Lee HY, Kim JH, Jeung HW, Lee CU, Kim DS, Li B, et al. Effects of *Ficus carica* paste on loperamide-induced constipation in rats. Food and Chemical Toxicology. 2012;**50**:895-902. DOI: 10.1016/j.fct.2011.12.001

[13] Han SH, Park K, Kim EY, Ahn SH, Lee HS, Suh HJ. Cactus (*Opuntia humifusa*) water extract ameliorates loperamide-induced constipation in rats. BMC Complementary and Alternative Medicine. 2017;**17**(1): 49-56. DOI: 10.1186/s12906-016-1552-8

[14] Méité S, Bahi C, Yéo D, Datté JY, Djaman JA, N'guessan DJ. Laxative activities of *Mareya micrantha* (Benth.) Müll. Arg. (Euphorbiaceae) leaf aqueous extract in rats. BMC Complementary and Alternative Medicine. 2010;**10**:7. DOI: 10.1186/1472-6882-10-7

[15] Guarize L, Costa JC, Dutra LB, Mendes RF, Lima IVA, Scio E. Anti-inflammatory, laxative and

intestinal motility effects of *Senna macranthera* leaves. Natural Product Research. 2012;**26**:331-343. DOI: 10.1080/14786411003754264

[16] Kim JE, Lee YJ, Kwak MH, Ko J, Hong JT, Hwang DY. Aqueous extracts of *Liriope platyphylla* induced significant laxative effects on loperamide-induced constipation of SD rats. BMC Complementary and Alternative Medicine. 2013;**13**:333-344. DOI: 10.1186/1472-6882-13-333

[17] Kumari M, Jain S. Tannins: An antinutrient with positive effect to manage diabetes. Research Journal of Recent Sciences. 2012;**1**(12):1-8

[18] Barbehenn RV, Peter Constabel C. Tannins in plant-herbivore interactions. Phytochemistry. 2011;**72**(13):1551-1565. DOI: 10.1016/j.phytochem.2011.01.040

[19] Hemingway RW, Karchesy JJ. Chemistry and Significance of Condensed Tannins. Vol. 113. London: Pleum Press; 2014

[20] Koleckar V, Kubikova K, Rehakova Z, Kuca K, Jun D, Jahodar L, et al. Condensed and hydrolysable tannins as antioxidants influencing the health. Mini Reviews in Medicinal Chemistry. 2008;**8**(5):436-447. DOI: 10.2174/138955708784223486

[21] Pinent M, Blay M, Blade MC, Salvado MJ, Arola L, Ardevol A. Grape seed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. Endocrinology. 2004;**145**:4985-4990. DOI: 10.1210/en.2004-0764

[22] Muthusamy VS, Anand S, Sangeetha KN, Sujatha S, Lakshmi BABS. Tannins present in *Cichorium intybus* enhance glucose uptake and inhibit adipogenesis in 3T3-L1 adipocytes through PTP1B inhibition. Chemico-Biological Interactions. 2008;**174**:69-78. DOI: 10.1016/j.cbi.2008.04.016

[23] Kirkea DA, Smyth TJ, Rai DK, Kenny O, Stengel DB. The chemical and antioxidant stability of isolated low molecular weight phlorotannins. Food Chemistry. 2011;**15**:1104-1112. DOI: 10.1016/j.foodchem.2016.11.050

[24] N'guessan K. Thèse de Doctorat 3ème cycle. Université d'Abidjan-Cocody, Botanique et biologie. Contribution à l'étude ethnobotanique chez les Krobou de la sousprefecture d'Agboville (Côte d'Ivoire). 1995

[25] Mac Foy CA, Cline EI. *In vitro* antibacterial activities of three plants used in traditional medicine in Sierra Leone. Journal of Ethnopharmacology. 1990;**28**:323-327, 90083-90086. DOI: 10.1016/0378-8741(90)

[26] Guede-guina F, Tsai CS, Smith MO, Vangah MM, Washington B, Ochillo RF. The use of isolated functional heart to pharmacologically characterize active ingredient in the aqueous extracts of *Mareya micrantha*. Journal of Ethnopharmacology. 1995;**45**:19-26. DOI: 10.1016/0378-8741(94)01190-B

[27] Abo KJ-C, Aka KJ, Ehile EE, Guede Guina F, Traore F. Effets cholinergiques d'un extrait aqueux brut de Mareya micrantha (Euphorbiacée) sur la pression et d'activité cardiaque. La Revue de Médecine et de Pharmacie. 2000;**5**:11-20

[28] Tsai CS, Guede Guina F, Smith MO, Vangah MM, Ochillo RF. Isolation of cholinergic active ingredients in aqueous extracts of *Mareya micrantha* using the longitudinal muscle of isolated Guinea-pig ileum as a pharmacological activity marker. Journal of Ethnopharmacology. 1995;**45**:215-222. DOI: 10.1016/0378-8741(94)01219-P

[29] Zirihi GN, Mambu L, Guédé-Guina F, Bodo B, Grellier P. *In vitro*

antiplasmodial activity and cytotoxicity of 33 West African plants used for the treatment of malaria. Journal of Ethnopharmacology. 2005;**98**:281-285. DOI: 10.1016/j.jep.2005.01.004

[30] Dosso M, Meite S, Yeo D, Traore F, Diaman AJ, N'guessan JD. Cholinergic and histaminergic activites of the aqueous extract of mareya micrantha (Benth) *Mareya micrantha* (Benth). Müll Arg (Euphorbiaceae). Asian Journal of Chemistry. 2013;**8**(1):24-32. DOI: 10.3923/ajb.2013.24.32

[31] Méité S, Bahi C, Yéo D, Datté JY, Djaman JA, N'guessan DJ. Laxative activities of *Mareya micrantha* (Benth.). Müll. Arg. (Euphorbiaceae) leaf aqueous extract in rats. BMC Complementary and Alternative Medicine. 2010;**10**. DOI: 7. DOI:10.1186/1472-6882-10-7

[32] Zahn M, Trinh T, Jeong ML, Wang D, Abeysingbe P, Jia Q. A revised-phase high performance liquid chromatographic method for the determination of aloesin A and anthraquinone of *Aloe ferox*. Phytochemical Analysis. 2007;**19**:122-126. DOI: 10.1002/pca.1024

[33] Githens TS. Drug Plants of Africa. Philadelphia: University of Pennsylvania Press; 1979. 50 p

[34] Kambizi L, Goosen BM, Taylor MB, Afolayan AJ. Anti-viral effects of aqueous extracts of *Aloe ferox* and *Withania somnifera* on herpes simplex virus type 1 in cell culture. South African Journal of Science. 2007;**103**:359-360

[35] Grierson DS, Afolayan AJ. An ethnobotanical study of plants used for the treatment of wounds in the Eastern Cape, South Africa. Journal of Ethnopharmacology. 1999;**67**:327-332. DOI: 10.1016/S0378-8741(99)00082-3

[36] Van Wyk B-E, Van Oudtshoorn B, Gericke N. Medicinal Plants of South Africa Pretoria. 2nd ed. South Africa: Briza Publication; 1997. 42 p

[37] Crouch NR, Symmonds R, Spring A, Diederichs N. Fact sheet for growing popular medicinal plant species. In: Commercializing Medicinal plants: A Southern African Guide. Stellenbosch: Sun Press; 2006. pp. 100-102

[38] Watt J, Breyer-Brandwijk MG. Medicinal and Poisonous Plants of Southern and Eastern Africa. 2nd ed. London: Livingstone; 1962

[39] Wintola OA, Afolayan AJ. Phytochemical constituents and antioxidant activities of the whole leaf extract of *Aloe ferox* Mill. Pharmacognosy Magazine. 2011;**7**(28):325-333. DOI: 10.4103/0973-1296.90414

[40] Wintola OA, Sunmonu T, Afolayan AJ. Toxicological evaluation of aqueous extract of *Aloe foerox* Mill. In loperamide-induced constipated rats. Human & Experimental Toxicology. 2011;**30**(5):425-431. DOI: 10.1177/0960327110372647

[41] Kapoor LD. Handbook of Ayurvedic Medicinal Plants: Herbal Reference Library. Australia: CRC Press Boca Raton; 1990. pp. 324-328

[42] Kirtikar KR, Basu BD. Indian Medicinal Plants. India: Periodical Experts Book Agency; 1988. 2331 p

[43] Baquar SR. Medicinal and Poisonous Plants of Pakistan. 2nd ed. Printas: Karachi; 1989. p. 61. 209-210

[44] Prajapati ND, Purohit SS, Sharma AK, Kumar T. A Hand Book of Medicinal Plants—A Complete Source Book. New Delhi: Agrobios; 2003. 32 p

[45] Usmanghani K, Saeed A, Alam MT. Indusyunic Medicine. Karachi: University of Karachi Press; 1997.

[46] Shenoy SR, Kameshwari MN, Swaminathan S, Gupta MN. Major antifungal activity from the bulbs of indian squill *Urginea indica* is a chitinase. Biotechnology Progress. 2006;**22**: 631-637. DOI: 10.1021/bp050305n

[47] Deepak AV, Salimath BP. Antiangiogenic and proapoptotic activity of a novel glycoprotein from *Urginea indica* is mediated by NF-kappaB and Caspase activated DNase in ascites tumor model. Biochimie. 2006;**88**:297-307. DOI: 10.1007/s11010-005-7717-2

[48] Abbas S, Bashir S, Khan A, Mehmood MH, Gilani AH. Gastrointestinal stimulant effect of *Urginea indica* Kunth. and involvement of muscarinic receptors. Phytotherapy Research. 2012;**26**(5):704-708. DOI: 10.1002/ptr.3634

[49] Mossa JS, Al-Yahya MA, AlMeshal IA. Medicinal Plants of Saudi Arabia. Riyadh: King Saud University Libraries Publications; 1987

[50] Popova ME, Simanek V, Dolejs L, Smysl B, Preininger V. Alkaloids from *Fumaria parviflora* and *Fumaria kralikii*. Planta Medica. 1982;**45**:120-122. DOI: 10.1055/s-2007-971259

[51] Rahman AU, Khati MK, Choudhary MI, Sener B. Chemical constituents of *Fumaria indica*. Fitoterapia. 1992;**63**:129-135

[52] Rehman N, Mehmood MH, Al-Rehaily AJ, Mothana RAA, Gilani AH: Species and tissue-specificity of prokinetic, laxative and spasmodic effects of *Fumaria parviflora*. BMC Complementary and Alternative Medicine. 2012;**12**:16. DOI: 10.1186/1472-6882-12-16

[53] Suau R, Cabezudo B, Rico R, Najera F, Lopez-Romero JM. Direct determination of alkaloid contents in Fumaria species by GC-MS. Phytochemical Analysis. 2002;**13**:363-367. DOI: 10.1002/pca.669

[54] Mehmood MH, Rehman A, Rehman N, Gilani AH. Studies on Prokinetic, laxative and spasmodic activities of *Phyllanthus emblica* in experimental animals. Phytotherapy Research. 2013;**27**:1054-1060. DOI: 10.1002/ptr.4821

[55] Majeed M, Bhat B, Jadhav AN, Srivastava JS, Nagabhushanam K. Ascorbic acid and tannins from *Emblica officinalis* Gaertn. fruits—A revisit. Journal of Agricultural and Food Chemistry. 2009;**57**:220-225. DOI: 10.1021/jf802900b

[56] El-Desouky SK, Ryu SY, Kim YK. A new cytotoxic acylated apigenin glucoside from *Phyllanthus emblica* L. Natural Product Research. 2008;**22**:91-95. DOI: 10.1080/14786410701590236

[57] Liu Q, Wang YF, Chen RJ, Zhang MY, Wang YF, Yang CR, et al. Anti-coxsackie virus B3 norsesquiterpenoids from the roots of *Phyllanthus emblica*. Journal of Natural Products. 2009;**72**:969-972. DOI: 10.1021/np800792d

[58] Thakur RS, Puri HS, Husain A. Major Medicinal Plants of India. India: CIMAP; 1989. Lucknow

[59] Krishnaveni M, Mirunalini S. Therapeutic potential of *Phyllanthus emblica* (amla): The ayurvedic wonder. Journal of Basic and Clinical Physiology and Pharmacology. 2010;**21**:93-105. DOI: 10.1515/JBCPP.2010.21.1.93

[60] Sharma A, Sharma MK, Kumar M. Modulatory role of *Emblica officinalis* fruit extract against arsenic induced oxidative stress in Swiss albino mice. Chemico-Biological Interactions. 2009;**180**:20-30. DOI: 10.1016/j.cbi.2009.01.012

[61] Srirama R, Deepak HB, Senthilkumar U, Ravikanth G, Gurumurthy BR, Shivanna MB, et al. Hepatoprotective activity of *Indian Phyllanthus*. Pharmaceutical Biology. 2012;**50**:948-953. DOI: 10.3109/13880209.2011.649858

[62] Bhatia J, Tabassum F, Sharma AK, Bharti S, Golechha M, Joshi S, et al. *Emblica officinalis* exerts antihypertensive effect in a rat model of DOCA-salt induced hypertension: Role of (p) eNOS, NO and oxidative stress. Cardiovascular Toxicology. 2011;**11**:272-279. DOI: 10.1007/s12012-011-9122-2

[63] Nicolis E, Lampronti I, Dechecchi MC, Borgatti M, Tamanini A, Bianchi N, et al. Pyrogallol, an active compound from the medicinal plant *Emblica officinalis*, regulates expression of pro-inflammatory genes in bronchial epithelial cells. International Immunology. 2008;**8**:1672-1680. DOI: 10.1016/j.intimp.2008.08.001

[64] Mehmood MH, Siddiqi HS, Gilani AH. The antidiarrheal and spasmolytic activities of *Phyllanthus emblica* Linn. Are mediated through dual blockade of muscarinic receptors and calcium channels. Journal of Ethnopharmacology. 2011;**133**: 856-865. DOI: 10.1016/j.jep.2010.11.023

[65] Zhong ZG, Luo XF, Huang JL, Cui W, Huang D, Feng YQ, et al. Study on the effect of extracts from the leaves of *Phyllanthus emblica* on immune function of mice. Zhong Yao Cai. 2013;**36**(3):441-444

[66] Kim JE, Go J, Koh EK, Song SH, Sung JE, Lee HA, Lee YH, Hong JT, Hwang DY. Gallotannin-enriched extract isolated from Galla Rhois may be a functional candidate with laxative effects for treatment of loperamide-induced constipation of SD rats. PLoS One. 2016;**11**(9):e0161144. DOI: 10.1371/journal.pone.0161144

[67] Lee SM, Lee JW, Park JD, Kim JI. Study on formation and development of *schlechtendalis chinensis* gall in *Rhus javanica*. Korean Journal of Applied Entomology. 1997;**36**:83-87

[68] Kim SH, Park HH, Lee S, Jun CD, Choi BJ, Kim SY, et al. The anti-anaphylactic effect of the gall of *Rhus javanica* is mediated through inhibition of histamine release and inflammatory cytokine secretion. International Immunopharmacology. 2005;**5**:1820-1829. DOI: 10.1016/j.intimp.2005.06.007

[69] Go J, Kim JE, Koh EK, Song SH, Seung JE, Park CK, et al. Hepatotoxicity and nephrotoxicity of gallotannin-enriched extract isolated from Galla Rhois in ICR mice. Laboratory Animal Research. 2015;**31**:101-110. DOI: 10.5625/lar.2015.31.3.101

[70] Lee JJ, Kim DH, Lim JJ, Kim DG, Min WG, Kim GS, et al. Anticoccidial effect of supplemental dietary Galla Rhois against infection with *Eimeria tenella* in chickens. Avian Pathology. 2012;**41**:403-407. DOI: 10.1080/03079457.2012.702888

[71] Cha CN, Yu EA, Park EK, Kim S, Lee HJ. Effects of dietary supplementation with Galla Rhois on growth performance and diarrhea incidence in postweaning piglets. Journal of Veterinary Clinics. 2013;**30**:353-358

[72] Ahn YJ, Lee CO, Kweon JH, Ahn JW, Park JH. Growth-inhibitory effects of derived tannins on intestinal bacteria. Journal of Applied Microbiology. 1998;**84**:439-443. DOI: 10.1046/j.1365-2672.1998.00363.x

[73] Chae HS, Kang OH, Choi JG, Oh YC, Lee YS, Brice OO, et al. Methyl gallate inhibits the production of interleukin-6

and nitric oxide via down-regulation of extracellular-signal regulated protein kinase in raw 264. 7 cells. American Journal of Chinese Medicine. 2010;**38**:973-983. DOI: 10.1142/S0192415X10008391

[74] Ata N, Oku T, Hattori M, Fujii H, Nakajima M, Saiki I. Inhibition by galloylglucose (GC6-10) of tumor invasion through extracellular matrix and gelatinase-mediated degradation of type IV collagens by metastatic tumor cells. Oncology Research. 1996;**8**:503-511

[75] Lee TY, Chang HH, Wang GJ, Chiu JH, Yang YY, Lin C. Water-soluble extract of *Salvia miltiorrhiza* ameliorates carbon tetrachloride-mediated hepatic apoptosis in rats. Journal of Pharmacy and Pharmacology. 2006;**58**:659-665. DOI: 10.1211/jpp.58.5.0011

[76] Korea Food and Drug Administration. The Korean Pharmacopeia. 11th ed. Seoul, Korea: Shinilbooks com; 2015

[77] Zhang L, Reddy N. Bioactive natural molecules and traditional herbs for life threatening diseases. Journal of Molecular Sciences. 2018;**2**(1):4. DOI: 10.155/2016/9872302