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Gastric acid inhibitory and gastric protective effects of *Cannabis* and cannabinoids

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ABSTRACT

Cannabis sativa has long been known for its psychotropic effect. Only recently with the discovery of the cannabinoid receptors, their endogenous legends and the enzymes responsible for their synthesis and degradation, the role of this 'endocannabinoid system' in different pathophysiologic processes is beginning to be delineated. There is evidence that CB_1 receptor stimulation with synthetic cannabinoids or *Cannabis sativa* extracts rich in Δ^9-tetrahydrocannabinol inhibit gastric acid secretion in humans and experimental animals. This is specially seen when gastric acid secretion is stimulated by pentagastrin, carbachol or 2-deoxy-D-glucose. *Cannabis* and/or cannabinoids protect the gastric mucosa against noxious challenge with non-steroidal anti-inflammatory drugs, ethanol as well as against stress-induced mucosal damage. *Cannabis*/cannabinoids might protect the gastric mucosa by virtue of its antisecretory, antioxidant, anti-inflammatory, and vasodilator properties.

1. Introduction

Cannabis is the most commonly abused illicit substance worldwide. The two commonly used *Cannabis* preparations are herbal *Cannabis* or marijuana (prepared from the dried flowering tops and leaves) and hashish (consists of dried *Cannabis* resin and compressed flowers). Both are derived from the female plant of *Cannabis sativa* Linn (family *Cannabidaceae*) [1]. Research into *Cannabis* led to discovery of its active constituents or cannabinoids, a terpeno-phenol compounds; more than 70 of which have been isolated. The most studied cannabinoids are Δ^9-tetrahydrocannabinol (THC), cannabinol, cannabidiol, cannabigerol, cannabichromene, Δ^9-tetrahydrocannabivarin, cannabidivarin and others [2,3]. Δ^9-THC is the primary constituent that is responsible for the psychotropic properties of recreational *Cannabis* [4].

Cannabinoids mediate their biological effects through interaction with cannabinoid receptors, which belong to the superfamily of G protein-coupled receptors. There are at least two cannabinoid receptor subtypes: the CB_1 receptor, essentially located in the central nervous system, but also in peripheral tissues, and the CB_2 receptor, found only at the periphery especially on immune cells [5]. Most of *Cannabis* effects in the central nervous system are mediated by CB_1 receptors. These are expressed at brain areas that control movements, memory, cognition and emotion and in the spinal cord [6,7] where they mediate retrograde inhibition of neuronal activity [8].

Cannabinoid receptors can also be activated by a number of endogenous ligands, the endocannabinoids. The main endocannabinoids, arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG) are selective agonists at the CB_1 and CB_2 receptors, respectively. Both are derivatives of arachidonic acid, that are produced and released 'on demand' by cleavage of membrane lipid precursors and are hydrolysed by the fatty acid amide hydrolase anandamide or monoglyceride lipase, respectively. Other endocannabinoids are noladin ether and virodhamine [9–11]. The cannabinoid receptors, endocannabinoids as well as the enzymes responsible for their synthesis or degradation, collectively constitute the 'endocannabinoid system' [12].

Cannabis sativa has a wide-world reputation as a psychotropic drug [1]. *Cannabis* is usually smoked, but may also be eaten, mixed in cakes or cookies or drunk in a liquid infusion [13]. Only recently, did *Cannabis* and cannabinoid-based medicines come to attention as a remedy for different medical conditions. The sublingual oromucosal spray Sativex, composed of whole plant extract containing both Δ^9-THC and cannabidiol (CBD) [THC:CBD = 1:1] have recently been approved for the treatment of pain and spasticity in multiple sclerosis [14].

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Dronabinol (Marinol) and nabilone (Cesamet) are two oral formulations of a synthetic THC approved for the treatment of nausea and vomiting that complicate chemotherapy and which are refractory to conventional antiemetic therapy. These agents are also being used to improve appetite to treat weight loss associated with human immunodeficiency virus infection and cancer [15]. Medicinal *Cannabis* is also being used for a variety of medical conditions including chronic pain, depression, arthritis, and neuropathy [16–18]. The endocannabinoid system is a target for the treatment of neurodegenerative disease *e.g.*, tics in Tourette syndrome, levodopa-induced dyskinesia in Parkinson s disease and some forms of tremor and dystonia [19,20].

Cannabinoid receptors and their endogenous ligands (anandamide and 2-arachidonoyl glycerol) have been identified in the gastrointestinal tract and are involved in mediation of several gastrointestinal functions *e.g.*, relaxation of the lower oesophageal sphincter, gastric acid secretion, gastric emptying, gastrointestinal motility and fluid secretion [21,22]. Evidence thus suggests that cannabinoid-based medicines might be beneficial in a number of gastrointestinal disorders.

The aim of this review is to compile and discuss the available data pertaining to the effect of *Cannabis* and/or cannabinoids on gastric acid secretion and gastric mucosal integrity.

2. *Cannabis* and gastric acid secretion

There are no clinical studies on the effect of *Cannabis* on gastric acid secretion. In their study, however, on 90 human volunteers participating in a vaccine development programme, Nalin *et al.* 1978 [23] found that smoking *Cannabis* for more than 2 days a week was associated with low gastric acid output. On the other hand, several preclinical studies suggested inhibition of gastric acid secretion by *Cannabis* or individual cannabinoids. Thus, in rats subjected to pylorus-ligation for (2–4) h (Shay rat), the administration of an ethanolic extract of *C. sativa* raised the gastric pH. Rats treated with 0.1 and 0.3 g/kg of *Cannabis* extract for 4 h had their gastric pH raised from 2 to 4 and 4.5. In the 4 h pylorus-ligated rat, *Cannabis* 1 g/kg raised pH slightly more than 0.05 g/kg of the histamine H-2 receptor blocker ranitidine. In rats subjected to pylorus-ligation for 2 h, ranitidine was more effective than *Cannabis* (pH values were 2.2, 3.5 and 4 for control, *Cannabis* and ranitidine, respectively) [24].

The effect of long-term treatment with *Cannabis* extracts rich in Δ^9-THC on gastric acid secretion was studied in the pylorus-ligated rat model (Shay rat). Rats were treated with 5, 10 and 20 mg/kg of *Cannabis* extract (expressed as Δ^9-THC) subcutaneously for 4 weeks and then subjected to pylorus-ligation (for 4 h) with or without gastric acid stimulation (using pentagastrin, histamine or carbachol). The administration of low doses of *Cannabis i.e.* 5 or 10 mg/kg Δ^9-THC stimulated basal gastric acid output and gastric volume. The high dose of 20 mg/kg, however, had no effect on basal gastric acid secretion. The effect of *Cannabis* on stimulated gastric acid secretion was somehow different in that it inhibited gastric acid secretory responses stimulated by pentagastrin or carbachol in a dose-dependent manner. On the other hand, *Cannabis* pretreatment had no significant effect on acid output stimulated by histamine [25].

Cannabis's most active constituent Δ^9-THC is CB_1 receptor agonist [6,7]. When administered intravenously (i.v.), synthetic CB_1 receptor agonists inhibited gastric acid secretion in the anaesthetized rat preparation. Thus, WIN55, 212-2, which is a non-selective cannabinoid agonist decreased gastric acid secretion stimulated by pentagastrin (10 mg/kg, *i.v.*) in anaesthetized rats. The inhibitory effect of WIN55, 212-2 on gastric acid secretion is likely to be mediated via CB_1 receptors, since selective CB_1 receptor antagonists SR 141716A and LY320135t antagonized its action. WIN55, 212-2, however, failed to affect basal gastric acid secretion [26].

Similar data were provided by Adami *et al.* [27] who reported inhibition of pentagastrin stimulated gastric acid secretion in anaesthetized rats with lumen-perfused stomach by the non-selective cannabinoid agonists WIN55, 212-2 and HU-210. Gastric acid secretion stimulated by 2-deoxy-D-glucose (a centrally acting secretagogue which stimulates gastric acid by increasing efferent vagus activity) is inhibited by the cannabinoid agonists, thereby suggesting a centrally mediated inhibition of gastric acid secretion by these synthetic cannabinoid agonists. But in contrast to their effect on gastric acid stimulation by pentagastrin or 2-deoxy-D-glucose, the two cannabinoid agonists did not affect acid secretion stimulated by histamine. The study pointed again to a role for CB_1 receptors in inhibition of gastric acid secretion by the synthetic cannabinoids since their effect was blocked by a CB_1 but not CB_2 receptor antagonist. Moreover, vagal involvement is suggested by finding that the inhibitory effect of HU-210 on pentagastrin-induced acid secretion decreased following bilateral cervical vagotomy and ganglionic blockade with hexamethonium.

Using rat isolated parietal cells, Rivas and Garcûa [28], however, reported inhibition of gastric acid secretion stimulated by histamine after high concentration of Δ^9-THC (20 μM). Basal gastric acid secretion was unaffected.

Experiments in the isolated mouse stomach indicated the ability of CB_1 antagonism to increase gastric acid secretion. Stimulation with ouabain (an inhibitor of Na^+/K^+-ATPase) increased gastric acid secretion (by releasing acetylcholine from cholinergic nerves). The addition of the CB_1 receptor antagonist SR 141716A further increased the ouabain-stimulated acid secretion. In contrast, the cannabinoid agonist WIN55, 212-2 was without effect [29]. These data suggest a role for CB_1 receptors in inhibiting gastric acid secretion.

The above *in vivo* and *in vitro* studies thus suggest that are CB_1 receptor stimulation with synthetic cannabinoids or *C. sativa* extracts rich in Δ^9-THC inhibits gastric acid secretion. Given the data suggesting that the CB_1 agonist THC reduces transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux [30], cannabinoid-based medicines might find utility in the treatment of peptic ulcer disease including reflux oesophagitis. Interestingly, a study on the symptoms of withdrawal in human marijuana smokers reported ‘Stomach pain’ on the fourth day of abstinence among the abstinence symptoms [31]. One might thus speculate that the stomach pain was due to a rebound increase in gastric acid secretion and/or increased mucosal sensitivity.

3. The site of action of *Cannabis*

The secretion of gastric acid is controlled at different neural, hormonal and paracrine levels. The parietal cells in the gastric glands are the cells secreting and releasing hydrochloric acid. The parietal cell bears receptors for acetylcholine, histamine, and gastrin, the major stimuli for gastric acid secretion. Cholinergic stimulation is carried out by acetylcholine released from

postganglionic (*i.e.* intramural) cholinergic neurons and binds to muscarinic M_3 receptors. Acetylcholine also stimulates acid secretion indirectly by activating muscarinic M_2 and M_4 receptors on somatostatin D cells coupled to inhibition of somatostatin secretion. Histamine which is released from enterochromaffin-like cells, binds to and activates histamine H_2 receptors located on parietal cells, is a powerful stimulus for gastric acid secretion as well as gastrin released from G cells of the pyloric antrum. Gastrin reaches parietal cells via the circulation and stimulates the parietal cell directly and also indirectly by releasing histamine from enterochromaffin-like cells. Gastrin release from antral gastrin cells is stimulated by gastrin releasing peptide and inhibited by somatostatin [32,33].

The precise site of action for *Cannabis* and/or cannabinoids in mediating inhibition of gastric acid secretion is yet to be elucidated. The presence of CB_1 cannabinoid receptor messenger RNA within the rat stomach was demonstrated in full-wall thickness preparations of rat oesophagus and stomach [34]. In the rat, CB_1 receptors are present in pre- and post-ganglionic cholinergic neural elements innervating smooth muscle, mucosal, and submucosal blood vessels [27]. Accordingly, it has been suggested that the gastric antisecretory effects of cannabinoids are mediated by suppressing the vagal drive through activation of CB_1 receptor located on the vagal efferent pathways to the gastric mucosa and not on parietal cells [35].

With the use of different techniques (immunohistochemical staining, Western blot, polymerase chain reaction), the presence of CB_1 receptor has been shown on the acid-secreting parietal cells within the gastric glands in biopsy samples from the gastric mucosa of patients with dyspeptic symptoms [36]. This suggested a role for CB_1 receptors in control of gastric acid production. *Cannabis* therefore might inhibit gastric acid secretion by a direct action on the CB_1 receptors located on parietal cells.

Cannabinoid CB_1 receptors are also abundant in the central nervous system [20]. Following absorption THC as well as other cannabinoids are distributed to all tissues and accumulate in fatty tissues and are slowly released thereafter [1]. Because of their lipophilic properties, cannabinoids can easily cross the blood-brain barrier and act on brain cannabinoid receptors [7,37]. There is also an evidence that the antiemetic action of THC (0.05–1.00 mg/kg *i.p.*) is due to an effect at CB_1 receptors in specific regions of the dorsal vagal complex [38]. It is thus possible that the gastric antisecretory effect of *Cannabis* or cannabinoids is due to a central rather than a peripheral site of action *i.e.* by decreasing central efferent vagus activity.

In their study, Adami *et al.* [39], however, have shown that the central (intracerebroventricular: i.c.v.) administration of the synthetic cannabinoid agonists, WIN55, 212-2 or HU-210, failed to inhibit basal gastric acid secretion or that stimulated by pentagastrin in anaesthetized rats with lumen-perfused stomach. This suggested that a peripheral rather than a central CB_1 receptor mechanism is likely to be involved in the inhibitory effect of cannabinoids on gastric acid section [39].

4. *Cannabis* and gastric mucosal damage

Several preclinical studies provided data that supports a protective effect for *Cannabis* or cannabinoids in the stomach. In rats, Δ^9-THC (100 mg/kg) given via subcutaneous or oral routes inhibited the development of gastric ulcers induced by pyloric-ligation (Shay rat) with the protective effect of Δ^9-THC being most evident following subcutaneous compared with the oral route of administration. Δ^9-THC decreased gastric juice volume but not free and total acidity [40].

In their experiments, De Souza *et al.* [41] demonstrated that treatment with a *C. sativa* extract was able to protect the rat stomach against restraint induced ulcers. Rats were treated with different doses of the extract (5.0, 10.0, 20.0, 40.0 and 60.0 mg/kg, *i.p.*) both 24 h and immediately before immobilization. Alternatively, the extract (40 and 60 mg/kg) was given for 20 d prior to immobilization. The percentage of rats with lesions decreased with acute treatment reaching 41.7% for the dose of 60 mg/kg *vs.* control value of 65.6%–82.7%. This contrasted with chronic administration where the percentage of rats displaying lesions was 94.7% *vs.* control value of 100%, indicating that no protection occurred. These results also demonstrated that chronic *Cannabis* injection for 20 d resulted in the development of tolerance to the mechanisms of the anti-stress ulcer effect of *Cannabis*. Interestingly, in unrestrained animals, treatment with *Cannabis* extract at 40 or 60 mg/kg was associated with the development of gastric ulceration. Thus, only in the presence of stress, did *Cannabis* prevented gastric lesions, but the effect is evident in the acute and not in the long-term treatment.

Other researchers have shown that 2 h pretreatment with Δ^9-THC (10 mg/kg, *i.p.*) prevented the gastric mucosal haemorrhagic streaks evoked by administration of the non-steroidal anti-inflammatory drug (NSAID) diclofenac in mice; the effect being attenuated by the CB_1 receptor antagonist rimonabant [42]. Subsequent experiments in mice showed that Δ^9-THC given via oral or intraperitoneal routes prior to diclofenac, decreased the development of gastric hemorrhagic streaks. Δ^9-THC given *i.p.* was more potent in reducing diclofenac-induced gastric ulcerations compared to the oral route. Thus while *i.p.* Δ^9-THC decreased diclofenac-induced gastric hemorrhages at a dose of 0.1 mg/kg and higher, the effect of orally given Δ^9-THC was evident at a dose of 2.5 mg/kg and above. However, at a dose of 10 or 50 mg/kg Δ^9-THC given via *i.p.* or oral route inhibited the development of lesions to almost the same extent. Moreover, there was no difference between 10 or 50 mg/kg Δ^9-THC given via *i.p.* or oral route in the degree of their ulcer preventive effect [43]. Using a simple ethanolic *Cannabis* extract, Wallace *et al.* [44] found that oral (but not systemic) administration resulted in a decrease in the severity of gastric damage caused by the NSAID naproxen. The extract was administered either orally at doses of 1, 3 and 10 mg/kg or *i.p* at a dose of 30 mg/kg 30 min prior to oral administration of naproxen and rats euthanized 3 h later. The authors found that oral pretreatment with *Cannabis* inhibited the development of gastric lesions. Complete protection occurred with the 10 mg/kg of *cannabis* extract, while at 3 mg/kg there was 80% inhibition of the lesions. In contrast, *Cannabis* at 10 mg/kg given via *i.p.* route was without effect. The gastroprotective effect of the extract (10 mg/kg, orally) was blocked by a CB_1 antagonist (but not a CB_2 antagonist) and thus CB_1-mediated [44]. The discrepancy between the oral and *i.p.* routes is not expected since orally administered THC has a reduced systemic bioavailability owing to gastric degradation with the presence of acids and extensive first-pass metabolism in the liver [1,45].

Studies have also assessed the effect of long-term treatment with *Cannabis* extract on the chemically-induced gastric damage. Rats received daily subcutaneous injections of Δ^9-THC rich *Cannabis* extract for 4 weeks prior to pylorus-ligation and oral

administration of either acidified acetylsalicylic acid or ethanol (96%). In these experiments, *Cannabis* given at 5, 10 and 20 mg/kg of *Cannabis* extract (expressed as Δ^9-THC) inhibited the development of gastric mucosal damage in a dose-dependent manner [25]. These data does not support that tolerance to the gastroprotective action of *Cannabis* develops after repeated administration.

Gastric mucosal protective effects have also been reported for synthetic cannabinoids as well as endocannabinoids. In their study, Germano *et al.* [46] provided data that the non-selective cannabinoid receptor agonist WIN55, 212-2 decreased stress-induced gastric ulcers in rats. The cannabinoid CB_1 receptor antagonist SR 141716A itself had no effect on stress-induced lesions. SR 141716A (but not by the cannabinoid CB_2 receptor antagonist SR 144528), however, reversed the protective effect of WIN55, 212-2, thus suggesting the involvement of CB_1 receptors.

A study by Dembiñski *et al.* [47] found that anandamide (a natural endogenous ligand for CB_1 receptor) given *i.p.* prior to water immersion and restrain stress decreased the development of gastric mucosal lesions. The synthetic CB_1 receptor antagonist AM 251 antagonized this effect of anandamide, suggesting that CB_1 receptors are involved. In the study of Rutkowska and Fereniec-Gołebiewska [48] ACEA (arachidonyl-2-chloroethylamide), the selective cannabinoid CB_1, was given (*i.p.*) 1 h prior to oral administration of acetylsalicylic acid and rats euthanized 3 h later. In this study, ACEA inhibited the development of gastric mucosal lesions due to the NSAID with almost total protection being observed after 5 mg/kg of ACEA. Meanwhile, the reference drug ranitidine at 60 mg/kg reduced gastric lesions to 5.6% of control value.

Shujaa *et al.* [49] provided data that activation of central cannabinoid receptors resulted in gastric mucosal protection. The authors found that anandamide (an endocannabinoid), its biologically stable analogue methanandamide and the synthetic agonist WIN55, 212-2 reduced the ethanol-induced gastric mucosal lesions. The protective effect was evident after either peripheral (intravenous) or central (i.c.v.) administration. Centrally administered CB_1 receptor antagonist reversed the effect of centrally administered anandamide and methanandamide while naloxone (a non-selective opioid receptor antagonist) reversed the effect of intravenously administered anandamide, methanandamide and WIN55, 212-2. Thus, central cannabinoid CB_1 and opioid receptors were involved in the gastric protection by cannabinoids.

Moreover, increasing the levels of endogenous cannabinoids resulted in gastric protection. Fatty acid amide hydrolase is an enzyme which catalyses the intracellular hydrolysis of the endocannabinoid anandamide and other bioactive lipid amides [50]. Using URB937, an inhibitor of FAAH, Sasso *et al.* [51] observed a reduction in both the number and severity of gastric lesions produced by indomethacin in mice. 2-arachidonylglycerol is degraded mainly by monoacylglycerol lipase, but also by fatty acid amide hydrolase [6,7,52].

Kinsey *et al.* [42] administered diclofenac (100 mg/kg, p.o.) to mice so as to induce gastric mucosal lesions. The authors found that pretreatment with JZL184 (an inhibitor of 2-arachidonoyl glycerol inactivation by monoacylglycerol lipase) attenuated diclofenac-induced gastric hemorrhagic streaks. Meanwhile, 2-AG administered *i.p.* 2 h prior to diclofenac failed to prevent the NSAID-induced gastric lesions. JZL184 significantly increased 2-AG in the stomach. Pro-inflammatory cytokines (IL-1β, IL-6, tumour necrosis factor-alpha) increased in the stomach of diclofenac-treated mice and these were mitigated by JZL184. Rimonabant, a CB_1 receptor antagonist (but not the CB_2 receptor antagonist SR 144528) antagonized the effect of Δ^9-THC, thereby, suggesting a CB_1 mechanism. Further experiments in mice given diclofenac showed that repeated daily injection of JZL184 for 6 d protected against gastric mucosal damage caused by the NSAID. In contrast to the effect of the high dose of the agent (≥16 mg/kg), there was no tolerance associated with the low dose (≤8 mg/kg) [53]. The above data collectively indicated that stimulation of the endocannabinoid system mediates gastric mucosal protection.

5. Mechanism (s) of gastric protection by *Cannabis*

The integrity of the gastric mucosa is maintained due to a balance between 'mucosal aggressive factors' and the so called 'gastric mucosal protective mechanisms' [54]. The gastric mucosa is constantly exposed to high concentrations of luminal acid. Other aggressive factors in the lumen are pepsins, bile refluxed from incompetent pyloric sphincter, bacteria, ethanol and drugs especially the non-steroidal anti-inflammatory drugs (NSAIDs) capable of inhibiting the synthesis of cytoprotective prostaglandins. The mucosa's ability to withstand acid and other injurious agents is due to several mechanisms collectively is known as the gastric mucosal barrier. The mucus-bicarbonate layer together with surface-active phospholipids barrier constitute the first line of defence or the pre-epithelial barrier. The surface epithelial cells capable of rapid turnover and migration (restitution) and releasing mucins, bicarbonate, phospholipids, prostaglandins, trefoil peptides form the second line of defence. Other important defence mechanisms of gastric mucosa are cytoprotective prostaglandins, mucosal sulfhydryl content, adequate mucosal blood flow, and sensory afferent innervations. The development of gastric mucosa damage implies a breach in the balance between aggressive and defencive factors [55–58].

It is thus obvious that the management of peptic ulcer disease involves removal or neutralizing aggressive factors especially gastric acid *e.g.*, via antacids or acid inhibitors acting on histamine H_2 receptors or the proton pump. Strengthening natural defences is another approach *e.g.*, with the use of drugs such as sucralfate or cytoprotective prostaglandins [59]. Protecting the gastric mucosa independently of gastric acid inhibition is termed cytoprotection. This term was originally introduced by Robert *et al.* [60] referring to the unique ability of prostaglandins to protect the gastric mucosa from noxious agents such as 0.6 N HCl, 0.2 M NaOH, 25% NaCl or 96% ethanol, independently of gastric acid inhibition. Gastric cytoprotection was also proved for small doses of antisecretory agents, retinoids and growth factors [61]. Clearly, since *Cannabis* and cannabinoid agonists have been shown to inhibit gastric acid secretion, the protective effect of *Cannabis* cannot be ascribed to a cytoprotective property.

Another mechanism by which the stomach resists the chemical-induced injury is adaptive cytoprotection. Here, exposure of the gastric mucosa to luminal diluted ulcerogens or mild irritants will result in less damage following later exposure to strong necrotizing agents [62]. Several mechanisms have been postulated to account for adaptive cytoprotection including endogenous prostaglandin synthesis, stimulation of mucus or

HCO_3 secretion, mucosal vasodilation [63], and release of calcitonin gene-related peptide from the sensory nerves [64]. *Cannabis* or cannabinoid agonists, administered via systemic routes, however, were able to exert protective effect [25,41,43,44,46] making adaptive cytoprotection an unlikely mechanism. It remains to be established whether *Cannabis* administered into the gastric lumen acts as a mild irritant and thereby protecting the stomach via adaptive cytoprotection.

The effects of *Cannabis* are, however, the sum of its constituents. There are more than 70 different cannabinoids and these may have effects that are synergistic with or antagonistic to Δ^9-THC effects [65,66]. Other important constituents are terpenoids and the flavonoids flavocannabiside [66]. One terpenoid that is beta-caryophyllene has been shown to inhibit the development of gastric lesions evoked by ethanol or 0.6 N HCl when given orally to rats [67].

6. *Cannabis* strengthen gastric mucosal defences

Several mechanisms are likely to account for the ability of *Cannabis* or individual cannabinoid agonists to protect the stomach against noxious injury. *Cannabis* and/or individual cannabinoids inhibit gastric acid secretion [24–27], thereby, lessening the ability of this most powerful aggressive factor to threaten the gastric mucosa. Studies also indicated that *Cannabis* administration increases mucus secretion in the gastric mucosa [25]. Mucus is secreted by the mucous neck and surface epithelial cells and plays an important role in protecting the surface epithelial cells from luminal acid and other injurious agents. Mucus retards diffusion of luminal acid into the mucosa and together with bicarbonate secreted by the epithelium forms a pH gradient with near-neutral pH at the surface of the mucosa [68,69].

Luminal pepsins constitute an important aggressive factor capable of digesting mucus and thereby increasing the susceptibility of gastric mucosa to other injurious factors [70]. Studies in pylorus-ligated rats treated with *Cannabis* extract for 4 weeks indicated that *Cannabis* did not affect basal pepsin secretion. *Cannabis*, however, decreased pepsin secretion when the stomach is stimulated with pentagastrin and carbachol. *Cannabis* also decreased pepsin secretion following ethanol administration in rats [25].

Reactive oxygen intermediates have been implicated in the development of gastric mucosal injury due to ischaemia/reperfusion, ethanol, NSAIDs, and bacteria [71]. *Cannabis* has been shown to decrease lipid peroxidation and to increase reduced glutathione content and catalase activity in gastric mucosa [25]. *Cannabis* also inhibited mucosal nitric oxide [25]. Although a vasodilator effect of physiological concentrations of nitric oxide help the mucosa to withstand noxious challenge, high concentrations are likely to have a damaging effect [72–74]. *Cannabis* thus might protect the gastric mucosa by virtue of an antioxidant action.

Mucosal inflammation plays an important role in the development of gastric ulcers and although initial inflammatory response to the gastric mucosa helps to minimize or limit tissue damage, an exaggerated or uncontrolled response is detrimental to the mucosal integrity [69,75]. *Cannabis* has been shown to inhibit the pro-inflammatory cytokine tumour necrosis factor-alpha in mucosal homogenates [25], an action which might help to minimize the extent of mucosal damage.

Cannabis thus exerts antioxidant and anti-inflammatory effects in the gastric mucosa. It is to be noted, however, that these actions of *Cannabis* were evident only when the gastric mucosa was challenged with increased acid secretion or after exposing the mucosa to noxious agents such as acidified aspirin and ethanol and were not apparent under basal conditions [25].

One important factor in determining the ability of the gastric mucosa to resist gastric acid and other noxious agents is gastric mucosal blood flow [57]. This has been inferred from studies showing that interference with the blood supply to the mucosa *i.e.* ischaemia resulted in the development of gastric mucosal damage or aggravated the extent of mucosal damage evoked by NSAIDs [76,77] or ethanol [78]. On the other hand, agents which increase gastric mucosal blood flow such as isoproterenol [79], vasodilator prostaglandins [80] or capsaicin-type agents [81–83] helped to protect against noxious challenge. In this context, data have been provided that the endocannabinoid anandamide increases gastric mucosal blood flow [47]. There is also an evidence for a vaso-relaxant action for methanandamide in rat gastric arteries. This effect was independent of cannabinoid receptors [84]. It is thus possible that a vasodilatory action is involved in the gastric protective effects of *Cannabis* and or cannabinoids.

7. Conclusions

Cannabis and/or individual cannabinoids inhibit gastric acid secretion. The inhibitory effect of *Cannabis*/cannabinoid agonists on gastric acid secretion is likely to be mediated via CB_1 receptors. The inhibitory effect might be mediated through activation of CB_1 receptor located on the vagal efferent pathways. There is also an evidence for a possible direct effect for *Cannabis* on the CB_1 receptors located on parietal cells. *Cannabis* could also inhibit secretion by decreasing central efferent vagus activity. There appears to be no densistization to the action of *cannabis* following long-term administration of the herb. *Cannabis* inhibits the development of gastric ulcers induced by pyloric-ligation (Shay rat), restraint induced ulcers, and NSAIDs. Exogenous administration of endocannabinoids or increasing the levels of endogenous cannabinoids resulted in a gastric protection. The gastroprotective effect of cannabis could be blocked by a CB_1 antagonist. Activation of central cannabinoid receptors results in gastric mucosal protection. *Cannabis* thus exerts antioxidant and anti-inflammatory effects in the gastric mucosa. It is possible that a vasodilatory action is involved in the gastric protective effects of *cannabis* and or cannabinoids. Cannabinoids-based medicines might find utility in treatment of peptic ulcer disease including gastroesophageal reflux.

Conflict of interest statement

The author declares that he has no conflict of interest.

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