Relegar a abordagem complexa em detrimento da abordagem reducionista prevalecente e tratar assimetricamente o conhecimento popular e científico envolve um grande risco. No que se refere ao conhecimento sobre o potencial terapêutico das plantas medicinais e de seus constituintes, isto poderia implicar na limitação da capacidade de compreensão da multidimensionalidade dos fenômenos e das estruturas biológicas, além de ocasionar a perda de uma grande quantidade de informações geradas a partir da relação ao longo dos tempos entre o homem e a natureza, podendo até mesmo contribuir para a extinção de culturas que não estão inseridas na sociedade industrial contemporânea.

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Mechanism of antiulcerogenic activity of semi-synthetic crotonin obtained from *Croton cajucara* Benth.

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Abstract

The bark of *Croton cajucara* Benth. is used in Brazilian folk medicine to treat gastrointestinal disorders. Trans-dehydrocrotonin (DHC) isolated from the bark of *Croton cajucara* has antiulcerogenic activity[25]. The presence of similar activity in semi-synthetic crotonin obtained from dehydrocrotonin from *Croton cajucara* was observed in gastric ulcer-induced models (HCl/ethanol, ethanol, indomethacin, stress and pylorus ligature). The aim of the present study was to assess the mechanisms involved in the antiulcerogenic activity of semi-synthetic crotonin. We investigated the effects of semi-synthetic crotonin on the response to histamine of right atria isolated from guinea pigs and on the response to carbachol of stomach fundus strips from rats. Semi-synthetic crotonin (3, 10 or 30 mM) induced a shift to the right in the concentration-response curves to carbachol in the isolated rat stomach at the pD_2 level (pD_2: 5.42±0.05, 5.76±0.061, 5.77±0.076, 6.48±0.012, respectively), without any alteration in the maximum response. Semi-synthetic crotonin also induced a shift to the right in the concentration-response curves to histamine in guinea pig right atria, pD_2 (5.54±0.06, 6.01±0.06, 5.89±0.06, 5.92±0.03) and (%) maximum response (80±6.18, 118±6.18, 114±6.18, 122±1.4), respectively. Thus, the protective effect of semi-synthetic crotonin on induced gastric lesions could be due to antagonism of histaminergic and cholinergic effects on gastric secretion.

Since the beginning of this century it has been recognized that ulcer disease of the upper gastrointestinal tract depends on two sets of conditions: the presence of acid and the presence of predisposing factors, collectively thought of as reduction of mucosal defense. Therapy in the foreseeable future will continue to have control of acid secretion and subsequent reversal of mucosal damage and inflammation[5]. According to these authors, available means of therapeutic regulation of acid secretion include alteration of neural influences by means of surgery and alteration of parietal cell second-messenger levels by receptor antagonists such as antimuscarinic or antihistaminic

agents and by acid pump inhibitors.

The use of plants for the treatment of medical disease is a very common practice in the Brazilian population[26]. Natural products of plant and mineral origin provide an alternative strategy for the treatment of peptic ulcer disease[15].

The bark and leaves of Croton cajucara Benth. (Euphorbiaceae), an Amazonian medicinal plant commonly called "sacaca", are used traditionally to treat a wide range of gastrointestinal symptoms[29]. The nor-clerodane diterpene trans-dehydrocrotonin (DHC) is present in sacaca bark as the major secondary metabolite suggesting an important role for this compound in the traditional preparation[25]. Previous studies have established the antiulcerogenic effect of DHC (25), probably by suppressing acid secretion through non-competitive antagonism with receptors involved in gastric acid secretion and by protecting the gastric mucosa by an increase of PGE2[6].

The presence of similar activity in semi-synthetic crotonin obtained from dehydrocrotonin from *Croton cajucara* was observed in models of gastric ulcer induced by HCl/ethanol, ethanol, indomethacin, stress and pylorus ligature[1].

Therefore, the aim of this study was to assess the possible mechanisms involved in these pharmacological properties by investigating the effect of the semi-synthetic crotonin on both the mechanism of gastric acid secretion and on the protection factors. We studied the effects of semi-synthetic crotonin on gastric acid secretion using separate preparations of histaminic and muscarinic receptors. We also investigated if the antiulcer effect of semi-synthetic crotonin could be mediated by prostaglandins as factors enhancing mucosal defense.

We have previously demonstrated the antiulcerogenic and cytotoxic properties of semi-synthetic crotonin obtained from dehydrocrotonin from *Croton cajucara* Benth. The semi-synthetic crotonin inhibits the gastric lesions induced in rats by ethanol and in mice by hypothermic restraint stress, ethanol/HCl, indomethacin and pylorus ligature; with respect to cytotoxicity, aging reduced the cytotoxic effects of crotonin on isolated hepatocytes, suggesting that P450-mediated crotonin biotransformation may lead to the formation of more toxic metabolites[1].

In the gastric mucosa, the source of histamine mediating acid secretion is currently considered to be the ECL cell[20]. Both gastrin and acetylcholine stimulate histamine release from these cells[18], explaining the prominent role played by histamine as a physiological stimulator of gastric acid secretion. The pharmacology of this H2-receptor has been extensively studied and specific antagonists have been synthesized that have proved to be of considerable interest in the treatment of ulcer diseases[2].

The antagonist property of the test compound (at concentrations of 3, 10 or 30 mM) on histaminergic receptors was determined by inhibition of the chronotropic effect of histamine in isolated guinea pig right atria. Our data showed that semi-synthetic crotonin (3 mM) produced a shift to the right in the concentration response curves to histamine in guinea pig right atria, suggesting that this compound may act as an H2 receptor antagonist (Figure 1).

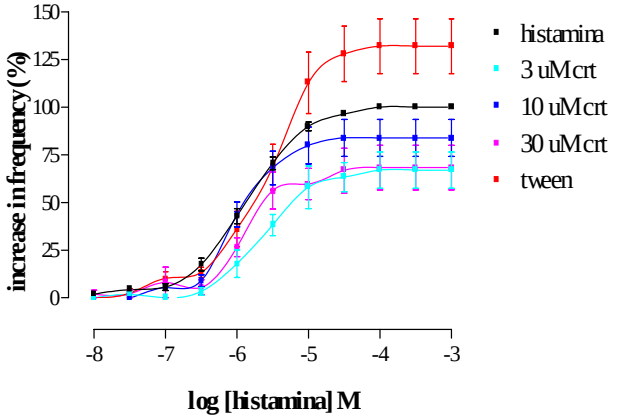


Figure 1. Cumulative concentration-response curves for histamine in the absence and presence of different concentration of semi-synthetic crotonin (crt). Each point represents the mean ± SEM.

The combination of rightward displacement of the concentration-response curve with depression of the maximal effect (Table 1) could be explained by impairment of the intracellular stimulus-transfer process by the antagonist.

Table 1. Maximum Response (MR), Basal Rate (BR) and pD2 to histamine, tween and semi-synthetic crotonin in guinea pig isolated atrium system.

Substance	Dose	Maximum Response (beats/min)	Basal Rate (beats/min)	pD_2	n
Histamine		122 ± 1.4	199 ± 0.95	5.92 ± 0.01	22
Tween	30 ml	134 ± 4.4	197 ± 3	5.6 ± 0.04*	7
Crotonin	3 mM	80 ± 6.2*	210 ± 4.2	5.54 ± 0.06*	5
	10 mM	118 ± 6.2	194 ± 4.2	6.01 ± 0.06	5
	30 mM	114 ± 6.2	192 ± 4.2	5.89 ± 0.06	5

Expressed as means ± SEM. ANOVA: F(4, 39) = 2.49 (MR); 0.566 (BR) and 3.531 (pD2) for $p<0.05$, followed by Dunnett's test, *$p<0.05$

Another important and extensively studied histaminergic receptor regulator of gastric secretion is the subtype H3. The role of H3-receptors in the regulation of gastric secretion remains unclear. Recent studies on enriched suspensions of ECL cells derived from rat and rabbit fundus indicate that histamine is capable of down-regulating its own synthesis and release via H3-receptors[18]. Preliminary studies confirming this hypothesis in rat mucosal fundic segments suggest that histamine and the selective H3-receptor agonist

acting via H3-receptors are capable of inhibiting somatostatin secretion thus, stimulating endogenous histamine secretion[22], and consequently acid secretion. Studies by Vuyyuru et al[31] showed that histamine stimulates acid secretion directly via H2-receptors on parietal cells as well as indirectly, via H3-receptors, suppressing somatostatin secretion and leading to a further increase in histamine secretion. Therefore, the semi-synthetic crotonin probably acts like a histaminergic receptor (H2) antagonist, blocking the main pathway of acid secretion stimulation, and/or H3, permitting the action of somatostatin on histamine secretion. One of the main stimulator of acid secretion from the parietal cell is acetylcholine, which stimulates acid secretion by interacting with a muscarinic receptor of the M3 subtype[7,2]. The cholinergic agents, in contrast to gastrin, do augment maximal histamine-stimulated acid secretion in the isolated rat stomach. The magnitude of parietal cell stimulation by histamine and acethylcoline may vary among species; however, the combination of the two secretagogues elicits a potentiating effect on the parietal cell[4].

The role of muscarinic receptors is mediated by interaction with G protein family members and, thus, by alteration induced by this protein in several effector molecule functions linked to the membrane. Subtypes M1, M3 and M5 activate a G protein (Gq/11), which is responsible for the stimulation of phospholipase C activity, so, that these receptors provoke Ca^{2+} dependent phenomenono like smooth muscle contraction and secretion[3].

To better study the action of semi-synthetic crotonin on the stomach muscarinic receptor longitudinal strips were obtained from the stomach fundus, a site with a large and a great portion number of oxyntic cells. The contractions induced by cumulative doses (104-M) of carbachol, a muscarinic agonist, were measured on the basis of 1 gf tension developed on the tissue.

Continuos cell stimulation with an agonist usually unsensitizes them, in such a way the effect is reduced after constant or subsequent exposure to the same drug. Therefore, the contracted smooth muscle relaxes spontaneously when the contractile agonist is removed[16]. On this basis, discontinuation of these drugs for a long period of time permits that the cell to "readjust" its response capacity, and the "recovery" of the response is usually be complete. After this "readjustment" the stomach was incubated for 1 h with following substances: 12% Tween 80, semi-synthetic crotonin (3, 10 or 30 mM) or pyrenzepine (10^6 M), in order to determined the type of binding to the muscarinic receptor.

The different treatments presented the same efficacy, represented by a maximum response (%) compared to the control group (Table 2); nevertheless, as proposed by the Stephenson theory[27], althoug there was no significant difference between the various treatments, the substances may occupy different percentages of the receptor population.

Table 2. Maximum response (MR) and pD_2 to carbachol, pirenzepine, tween and semi-synthetic crotonin in rat isolated gastric fundus

Substance	Dose	Maximum Responsem N/100mg	pD_2	n
Carbachol	$1x10^4$ M	19.7 ± 0.38	6.48 ± 0.01	25
Pirenzepine	$1x10^6$ M	19.2 ± 1.94	5.04 ± 0.06**	5
Tween	30 ml	15.6 ± 1.94	5.40 ± 0.06**	5
Crotonin	3 mM	10.5 ± 1.61	5.42 ± 0.05**	6
	10 mM	30.3 ± 1.94	5.76 ± 0.06**	5
	30 mM	11.1 ± 2.42	5.77 ± 0.07**	4

Expressed as means ± SEM. ANOVA: F(5, 44) = 2.955 (MR) and 31.397 (pD2) for p<0.05, followed by Dunnett's test, **p<0.01

Semi-synthetic crotonin produced a shift to the right of the carbachol concentration-response curves in the isolated rat stomach (Figure 2), without any alteration in the maximum response, acommon effect of antagonists that link reversibly to the receptor. According to Stephenson, the classic competitive antagonists have zero efficacy, which is confirmed by the non-significant results represented by the maximum response.

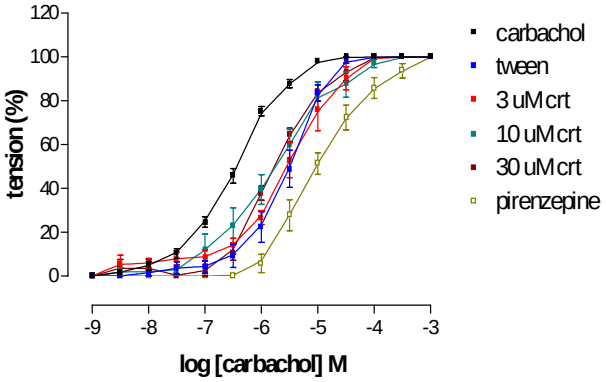


Figure 2. Cumulative concentration-response curves for carbachol in the absence and presence of different concentration of semi-synthetic crotonin (crt). Each point represents the mean ± SEM.

Studies by Lin et al[12] indicate that the expression of muscarinic receptor subtypes differs between tissues, showing that M2 and M3 receptors are widely distributed in gastrointestinal smooth muscle cells. Muscarinic receptor subtypes were shown to display differences in the intracellular signaling mechanisms.

Thus, the M3 receptor appears to regulate positively the phospholipid metabolism and intracellular Ca^{2+} in the parietal cells[17].

Since semi-synthetic crotonin reduces The of muscle contraction, we may suggest that this compound acts like a muscarinic receptor antagonist, probably the M3 subtype. Studies[32] with rabbit antral G-cells in primary culture confirm the gastrin release through stimulation by acetylcholine receptor agonists. The utilization of atropine, which has high affinity for glandular muscarinic M3 receptors, completely inhibited the gastrin release induced by carbachol, a stable acetylcholine analogue. This pharmacological profile suggests that muscarinic stimulation of gastrin release from antral G-cells is mediated via muscarinic M3 receptors. Thus, semi-synthetic crotonin may be interacting with the M3 receptor of G cells, interrupting or obstructing one of the main pathway sof acid secretion stimulation.

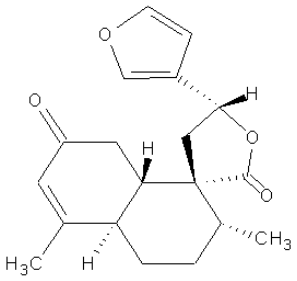
Another subtype of muscarinic receptor widely studied is M1. Shamburek et al[23] stated that the muscarinic M1 receptors are located predominantly on intramural postganglionic neurons, mediating the effects of ganglionic transmitters by the release of stimulatory substances, such as acetylcholine. These observations are consistent with recent findings[8] that there exist at least two types of neuronal (M1 e M2) muscarinic receptors that modulate acetylcholine release from cholinergic neurons.

For this reason, we may speculate that muscarinic M1 receptor blockade by semi-synthetic crotonin, for example, would permit the activation of other stimulatory muscarinic receptors or facilitate non-cholinergic stimulation by modulation of sympathetic ganglia or autoreceptors, supporting data reported by Mertz-Nielsen et al[13], who demonstrated that muscarinic M1 receptor blockade with pyrenzepine significantly increases gastric PGE2 output in humans. In addition, these investigators have previously observed that muscarinic M1 receptor inhibition increases gastric PGE2 synthesis during acid exposure[14]. Theoretically, such effects are potentially beneficial and may contribute to the gastroprotective effects of semi-synthetic crotonin.

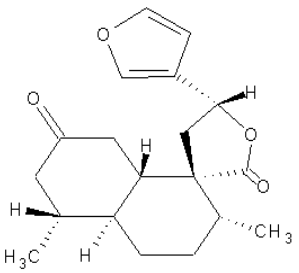
Material and Methods

Male Wistar rats weighing 150-250 g from the Centro de Bioterismo of the Universidade Estadual de Campinas (UNICAMP) were used. Male guinea pigs (250-350 g) from the ANILAB were also used. The animals were fasted prior to all assays involving the stomach because standard drugs or semi-synthetic crotonin were always administered orally (by gavage - 10 ml/kg) using a 12% solution of Tween 80 as vehicle. Animals received a certified Nuvilab CR-a® (Nuvital) diet and water ad libitum under standard conditions of 12h dark-12h light, humidity (55%) and temperature (22 ± 1 ºC).

The bark of *Croton cajucara* Benth. was collected from an experimental plantation in Benfica, near Belém, in the state of Pará, Brazil, and was identified by Dr. Nelson A. Rosa. A voucher herbarium specimen was deposited in the herbarium of the Museu Paraense Emílio Goeldi (accession number 247). Trans-dehydrocrotonin (DHC) was isolated from the bark as described by Souza Brito et al[25]. To obtain trans-crotonin, 12 g DHC were submitted to reduction at room tempetature during 12 h with 4 atm H_2, $CHCl_3$ as solvent and Pd (10%) as catalisator. The reaction product was purified in a silicagel 60 column (50x3 cm) eluted with a mixture of hexane/AcOEt (75/25) using air pression of 4 psi to mantain the eluent flux around 30 ml/min and colecting 33 fractions of 50 ml. Pure trans-crotonin was isolated in the fractions 3 to 13, showing only one spot in several TLC conditions and presenting very good accordance with the published physicochemical properties of the natural diterpene[7]. The semi-synthetic crotonin, classified as 4SRC, remained trans at the junction of rings A and B (Figure 3):



(A) Dehydrocrotonin



(B) Crotonin or 4SRC

The experiment of isolated guinea-pig right atria was conducted as previously described by Krielaart et al[11]. Male guinea-pigs were killed by cervical dislocation. Hearts were immediately removed and dissected and the atria were mounted under 0.5 g resting tension in 20 ml organ baths containing Krebs-Henseleit solution oxygenated with 95% O_2-5% CO_2 at 36.5±0.1 ºC. The increase in heart rate (beats min-1) induced by histamine in a cumulative dosing schedule was measured with an isometric transducer (Narco Bio-System) coupled to a polygraph (Narco Bio-System). The β-adrenoceptors were blocked with 1 mM propanolol previously added to the Krebs-Henseleit solution. After obtaining the cumulative dose-response curve for histamine the preparations were washed for 1 h with four changes of bathing solution. The atria were pre-equilibrated with one of three different concentrations of semi-synthetic crotonin (3, 10 or 30 mM) or 12% Tween 80 (30 ml) for 60 min before determination of another dose-response curve for the same agonist.

The experiments of isolated rat fundus stomach were performed according to the method described by Korolkiewicz et al[10]. Animals were killed by cervical dislocation. The abdomen was opened by a midline incision, the stomach excised, and the fundus dissected out and cut into longitudinal strips according

to the method described by Vane[30]. The strips were placed in Krebs-Henseleit solution as described for the atrium experiment. One end of the strip was attached to a fixed support and the free end to a lever connected to an isometric transducer coupled to a polygraph. The contractions induced by carbachol were measured as the tension developed by the tissue. Tissues were left to equilibrate for 30 min before the beginning of the experiment. The nutritive solution was changed every 15 min, except during the 1 h of contact with the semi-synthetic crotonin (3, 10 or 30 mM), pyrenzepine (10-6 M) or 12% Tween 80 (30 ml). Dose-response curves for carbachol were obtained in the absence and presence of different concentrations of test drugs.

Statistical Analysis

Results are expressed as means ± S.E.M. Statistical significance was determined by the Student "t" test and by one-way analysis of variance followed by the Dunnett test, with the level of significance set at $p<0.05$. All statistical analyses were performed using the Statistic 5.1 software (StatSoft, Inc.).

Acknowledgements

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Thermal behavior of biflorin by beans TG and a DSC photovisual system

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Abstract

This work proposes thermal characterization, of the biflorine, orto-quinon of *Capraria biflora* L., through the TG and DSC photovisual data. The thermogravimetric results showed that the decomposition reaction biflorine occurs three steps under air atmosphere, The DSC of biflorin presented five peaks relating to phase transitions. The DSC photovisual system demonstrated changes in biflorin.

Thermal behaviour studies in which thermal techniques are applied to naturally occurring substances are rather scarce in the literature[1,5].

Biflorin, a orto-quinon, (Figure 1) is constituent of the root of *Capraria biflora* L. (Scrophulariaceae). This plant is popularly is known as “chá da terra”, “chá da américa”, “chá das antilhas” and “chá da calçada” a plant used extensively in Northeast Brazil as antibiotic in the treatment of infections for fungi, dhermatofilus, yeasts and bacterias[6,10].

The present work deals with a thermal behavior of biflorin by means of TG and a DSC photovisual system.

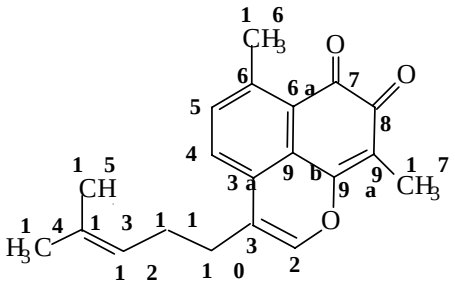

Figure 1. 3-prenyl-6,9-dimetil-7,8-dioxoquinon (biflorin).

Results and discussion

The TG curves of the biflorine (Figure 2, curve 1) presents three thermal decomposition stages, with temperature

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