

Pharmacological Actions of *Ananas comosus* L. Merrill: Revision of the Works Published from 1966 to 2020

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ABSTRACT

Bromeliaceae family is very common in Brazilian territory, with approximately 56 genera registered. *Ananas comosus* (L.) Merr, known as pineapple, one of the most consumed tropical fruits in the world, is the most studied species among them. Additionally some of the plants in this family are used to treat several pathologies in traditional medicine, so this study synthesizes the main pharmacological or biological actions of *A. comosus* and its varieties. A literature review was conducted from the main indexed databases (PubMed, SciELO, Science Direct, Lilacs) about the biological activities of the species *A. comosus* and its varieties. The *Ananas comosus* var. *comosus* was the most cited in the research, we found different secondary metabolites, mainly flavonoids, phenolic compounds and also the complex of enzymes bromelain which were mainly responsible for the fifteen pharmacological activities found, such as abortive, antioxidant activity, hypolipidemic and hypoglycemic. The results obtained in this work show that the species presents several pharmacological applications that can be exploited as a source for new chemical and biological studies that lead to the isolation of promising substances.

Key words: Bromeliaceae, Bromelioideae, Chemical Composition, Medicinal Plants, Pharmacological Activities, Pineapple.

INTRODUCTION

The use of medicinal plants and phytotherapies has occurred since ancient times, it is essential in the discovery of new medicines and have been contributed significantly to humanity. They are capable of treating several pathologies acting as antibacterial, antiparasitic, immunosuppressive and anticancer.^[3] The huge potential for the development of medicines produced directly from biologically active natural or synthetic products that use the chemical structure of the natural product as a base, given that the main entities currently developed are chemotherapeutic and antimicrobial.^[1,2]

Considering the variety of existing plants, phytochemical studies associated with biological assays represent a promising approach in the discovery of new drugs and for the rational use of biodiversity elements. In addition, it is possible to verify the use of plants as a therapeutic resource from ancient times to the current day.^[4,5] Brazil has an invaluable source of natural resources to obtain drugs, although the pharmacological potential of our native species have been poorly studied.^[6]

In Brazilian territory, Bromeliaceae's family is very common. It includes approximately 78 genera and about 3663 species, which are divided into subfamilies: Pitcairnioideae, Bromelioideae,

Tillandsioideae, Brocchinioideae, Hechtioideae, Lindmanioideae, Navioideae and Puyoideae. About 38% of the total Bromeliaceae species are in Brazil, with 56 genera registered in the national territory. *Ananas comosus* (L.) Merr. is the most studied species among them, also known as pineapple, it is one of the most consumed tropical fruits in the world.^[7] Commonly, some of the plants in this family are used to treat several pathologies in traditional medicine, presenting different pharmacological activities, such as diuretic, antimicrobial, anthelmintic, antitussive, antidiabetic and others. In addition to reports of bromelain enzyme and cysteine proteases, various special secondary metabolites such as triterpenes, steroids, flavonoids, glycerols, cinnamic acid derivatives, among others, were reported.^[7,8-10]

Thus, knowing the richness of the Bromeliaceae, due to the presence of the mentioned metabolites and studies that report the various medicinal properties, it's essential to carry out research identifying the main biological or pharmacological activities in *A.comosus* and its varieties, correlating with the substances responsible for the activity.

This study aimed to conduct a review to summarize the main pharmacological or biological actions of varieties of this species, indicating, when possible, the identified components of each variety, described in the literature. It is expected that this review

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may provide a starting point for future research focusing on chemistry composition and biological activities of this genera.

MATERIALS AND METHODS

An integrative review of the biological activities of *A. comosus* and its varieties in publications cataloged in PubMed, SciELO, Science Direct, Lilacs, using as keywords: *Ananas*, *Ananas comosus*, biological activities, pharmacology and phytotherapy was carried out from August 2017 to November 2020. Articles citing *Ananas comosus* or pineapple and its varieties, uses for therapeutic purposes in the treatment against different pathologies that were cited in more than one work, bibliographic surveys that addressed the pharmacological use of *A. comosus* were used as inclusion criteria. Exclusion criteria were non-scientific texts, only a work that cited a certain biological / pharmacological activity. For evaluation and adequacy to the inclusion or exclusion criteria, critical reading of the selected material was performed. After that, 100 articles were selected to compose the results.

RESULTS AND DISCUSSION

We found 100 studies dating from 1966 to 2020, which reported the use of *A. comosus* for the following activities: abortion; anticholinesterase; anticancer, anticoagulant; antidepressant, antihelminthic; antimicrobial; antioxidant; antiplasmodic; antirheumatic; cardioprotective; hypoglycemic, hypolipidemic, hepatoprotective, burns treatment and respiratory tract diseases. Among the selected research, the main ones were *in vitro* and *in vivo* studies and some ethnobotanical surveys. Regarding the substances responsible for the activities, there are mainly bromelain, phenolic compounds and some triterpenes and steroids. The species and varieties found were: *A. comosus* and *A. comosus* var. *bracteatus*. The main parts of the plant used were the leaves and fruits, followed by the peel. Table 1 presents the main information found in *A. comosus*.

Abortive effects, antilutotropic and antiovolatory

Studies assessing the ability of *A. comosus* to terminate pregnancy are old, evaluated the isolated substances ergosterol peroxide, β -sitosterol, 5-stigmastene-3 β ,7 α -diol, 5 α -stigmastane-3 β , 5,6 β -triol, 3 monobenzoate from pineapple leaf extracts and also they identified that when administered in rats it showed abortifacient activity.^[11,12] The compounds: ergosterol peroxide, β -sitosterol, 5-stigmastene-3 β -7 α -diol, 5 stigmastene-3 β -7 α -diol, 7-Oxo-5-stigmastene-3 β -ol, 5 α Stigmastene-3 β , 5, 6 β -triol extracted with petroleum ether and benzene from *A. comosus* leaves exerted abortive activity. Since the first day of administration it can be detected, but ergosterol peroxide showed the maximum abortifacient effect between 6 and 7 days of pregnancy, and action postponed from 13-16, after implementation.^[13] A more recent work performed, using 16 pregnant albino rats, which evaluates the abortive activity of the pineapple juice in two repeated tests, showed that, although the abortion was not provoked, it has potential. The animals presented contractions similar to oxytocin, thus it is possible the abortion act as well as the drug.^[14] Some mechanisms pointed these steroids as the main substances responsible for *A. comosus* abortive action. According to the author, *A. comosus* crude fruit extract has dose dependent effect with the content of serotonin present in *A. comosus*, this substance is responsible for uterine motility in different species.^[15]

According to studies conducted in rats and rabbits^[11,12,16-19] steroid 5 α -stigmastene-3 β , 5,6 β -triol 3-monobenzoate also exhibit antilutotropic and antiovolatory activity.

In order to investigate the tocolytic properties of *Ananas comosus* extract, many researchers use mice and human uterine tissue *in vitro* assays. It was observed that ethyl acetate extract produced a non-selective

inhibitory response on oxytocin, prostaglandin F2 α , acetylcholine and KCl. Furthermore, the authors concluded that the extract acted by multiple mechanisms as antagonism of Ca²⁺ type L channels, interfering in intracellular Ca²⁺ release mechanism, and releasing nitric oxide, characterize the extract as a promising candidate to be developed as a tocolytic agent.^[17]

Several ethnobotanical studies realized showed the use of *A. comosus* leaves and fruits by the India's population, being used as leaf tea or fruit juices, accompanied or not by other ingredients for birth and fertility control.^[20-22]

Anti acetylcholinesterase

Different studies report that plant extracts have inhibitory activity of the acetylcholinesterase enzyme (AChE).^[23,24] An *in vitro* study using extracts of fruits from *A. comosus*, showed that only the aqueous extract showed 4.3% inhibition,^[25] it is considered low activity if evaluated according to Vinhuta et al.^[23] However, as a controversial result compared to this previous one, the neuroprotection was evaluated using bromelain in an *in vivo* study in mice. The enzyme provided neuroprotection by decreasing oxidative stress and increasing cholinesterase.^[26] It is remarkable that this work was carried out *in vivo*, using only the enzyme bromelain, which may present different results from *A. comosus* extract from previous *in vitro* studies.

Hepatoprotective activity

The hepatoprotective activity of ethanolic and aqueous extracts from *A. comosus* fruits in an animal model, which hepatotoxicity was alcohol-induced. According to the authors, the antioxidant property of *A. comosus*, due to the presence of terpenoids, polyketides, amino acids, peptides, proteins, carbohydrates, lipids and polyphenolic compounds found in ethanolic and aqueous extracts, is responsible to hepatoprotective activity of this species. Despite this, more studies are necessary to clarify which phytochemicals are responsible for this organo-protective activity.^[27]

According to the literature, pineapple protects the liver by promoting a reconstructive effect on the hepatic metabolism, but not the kidneys intoxicated by damage induced by paracetamol in rats.^[28,29] Oral administration of pineapple vinegar can reduce the levels of serum enzyme biomarkers, such as alanine transaminase (ALT), aspartate transaminase (AST) and triglycerides (TG) after 7 days of treatment with paracetamol. Its also restored the levels of liver antioxidants, reduced the expression of inflammatory factors and the expression of cytochrome P450 protein in the liver in liver damage induced by paracetamol in mice.^[30] Corroborating these data, ethanolic and aqueous extracts from *Ananas comosus* fruits can decrease ALT and AST levels in rats poisoned by isoniazid after four weeks of treatment. The authors conclude that pineapple juice has hepatoprotective activity by inhibiting the widening of the central venous diameter, although analysis of the data has shown that liver function in these rats was not as good as in positive controls.^[31] These studies are relevant since they assess the pineapple's potential as a possible adjunct to treatment with drugs such as isoniazid and paracetamol, possibly minimizing its hepatotoxic side effects.

Antitumor

According to Table 1, it is possible to verify that this Bromeliaceae's species presents studies that relate its use as an antitumor, and indicate that the bromelain presence in *A. comosus* as the main agent of such activity.^[32-36] Bromelain stimulates the body's defense mechanism against cancer by increasing the cytotoxic activity of monocytes and macrophages, its inhibit cancer growth, acting as an immunomodulator, it is also used to treat leukemia and pulmonary metastasis.^[32,36]The

Table 1: Pharmacological activities presented in *Ananas comosus*.

Pharmacological activities	Species	Country	Part used	Substances	Authors
Abortive	<i>Ananas comosus</i>	India, Nigeria.	Leaves and fruits	Ergosterol peroxide, β -sitosterol, 5-stigmasten-3 β , 7a-diol, 5 stigmasten-3 β -7 β -diol, 7-Oxo-5-stigmasten-3 β -ol, 5a-stigmastan-3 β , 5, 6 β -triol, 3 monobenzoate.	[11-15,17,20,21,22,92,105,93,94]
Anticholinesterase	<i>Ananas comosus</i>	Brazil, Korea, India.	Leaves and fruits	----- Bromelain	[25,26]
Anticancer	<i>Ananas comosus</i>	USA, India.	Peel	Bromelain and other enzymes.	[32-36]
Anticoagulant	<i>Ananas comosus</i>	USA, Philippines.	-----	Bromelain	[35,39]
Antidepressant	<i>Ananas comosus</i>	India, Pakistan.	Peel	Quercitrin, narigenin, saponins and monoamines	[43,44]
Anthelmintic	<i>Ananas comosus</i>	Brazil, India.	Stem and peel	Bromelain and other substances.	[45,48,49,50,95,46,47]
Antimicrobial	<i>Ananas comosus</i>	Argeria, India, Nigeria.	Peel and leaves	-----	[96,52,53,54]
Antioxidant	<i>Ananas comosus</i> <i>Ananas comosus</i> var. <i>bracteatus</i>	Bangladesh, Brazil, India, Serbia	Leaves, fruit, peel and pulp.	Flavonoids and phenolic compounds	[56,97,55,56,98-101]
Antiplasmodial	<i>Ananas comosus</i>	Cameroon, Ghana, Nigeria.	Leaves	----- ----	[60-62]
Antirheumatic	<i>Ananas comosus</i>	Italy, India	Peel	Bromelain, flavonoids and tannins	[63,64]
Cardioprotective	<i>Ananas comosus</i>	India	Fruits	----- -----	[65,66]
Hypoglycemic / Hypolipidemic	<i>Ananas comosus</i>	Saudi Arabia, Brazil, China, India, Pakistan and Peru.	Fruits and leaves	Phenolic compounds	[67,68,69,71,72,70,73, 74,75,76,77]
Hepatoprotective	<i>Ananas comosus</i>	India.	Fruits	terpenoids, polyketides, amino acids, peptides, proteins, carbohydrates, lipids and polyphenolic compounds	[27-31]
Respiratory system diseases	<i>Ananas comosus</i>	Brazil, USA, Mauritius, India.	Leaves and fruits	Bromelain	[81,102,103,82, 104,83,80,87]
Burn treatment	<i>Ananas comosus</i>	-----	-----	Bromelain	[84,85,86]

cytotoxic activity of *A. comosus* pulp and peel was verified with *Artemia salina*, its showed LC_{50} 25 $\mu\text{g.mL}^{-1}$ and 29,6 $\mu\text{g.mL}^{-1}$ respectively.^[37] Thus, it is possible to corroborate the cytotoxic activity of *A. comosus* with possible antineoplastic activities, considering the toxicity low to LC_{50} above 500 $\mu\text{g.mL}^{-1}$; moderate to 100 to 500 $\mu\text{g.mL}^{-1}$ and high to LC_{50} below 100 $\mu\text{g.mL}^{-1}$.^[38]

Anticoagulant

The availability of *A. comosus* and the various activities of bromelain had led to the evaluation of this enzyme as anticoagulant.^[35,39] Among four extraction methods used, 95% ethanol extraction by maceration, Soxhlet using Analytical Grade Petroleum Ether, Expression with Spiral Twist and Decoction, first extract showed the ability to prevent blood clotting. This activity was obtained using different volumes of extract in the sample with human blood that was observed for 1-3 using and

its ability to prevent blood clotting was evaluated. The results obtained were comparable to EDTA, the positive control; however, further studies are necessary relating to the subject.^[39] Several studies have provided useful information for the development of new pharmacotherapies using medicinal plants to treat depression. Some species as *Hypericum perforatum*, *Vicia sojakii* and *Hibiscus esculentus* can act as important sources of new antidepressant drugs, furthermore *A. comosus* has an interesting potential as antidepressant agent.^[40-42]

Antidepressant potential

In order to evaluate the antidepressant potential of *A. comosus*, its juice was tested at different concentrations using albino mice and wistar rats, concentrations ranged from 5 to 20% and the period from 15 to 18 consecutive days of administration. The evaluation of antidepressant activity was verified using forced swimming test (FST), tail suspension

test (TST) and reserpine-induced hypothermia, compared to antidepressants fluoxetine (20 mg kg⁻¹) and imipramine (15 mg kg⁻¹). The authors concluded that *A. comosus* juice presented results comparable to antidepressants, showed reduction of immobility time, reversing hypothermia, as well as inhibition of brain monoamine activity.^[43]

The antidepressant activity in mice of the methanolic extract of *A. comosus* peels using three different doses compared to imipramine, FWT and TST were also performed. The extract has excellent low-dose antidepressant potential, but its effect on long-term administration and the safety profile in acute and chronic administration should be evaluated. Moreover, according to the same study, the presence of quercitrin, narigenin, rutin, saponins, and the numerous brain monoamines, such as serotonin, norepinephrine and dopamine, may contribute positively to their antidepressant effect.^[44]

Antiparasitic

Ananas comosus species has different uses in folk medicine, but also has uses in veterinary medicine, mainly as anthelmintic, being one of the causes of reduced productivity in livestock.^[45,47] The scientific validation of antiparasitic effects and possible side effects of plant products in ruminants were evaluated by different *in vitro* and *in vivo* methods of the activity of various plants, including *A. comosus*.^[45,48,49,50,46,47] *In vivo* studies showed that treatments using plant, in most cases, resulted in reductions in parasitism level, however, its not compared with anthelmintic drugs.^[45] On the other hand, the species in question evaluated against, the *Rhicephalus microplus* parasite and the *Haemonchus contortus* helminth, regarding the parasite, showed activity and with respect to helminth the activity *in vitro* was high and despite having *in vivo* activity, it was less significant. Further studies are necessary to prove the antiparasitic activities of the species.^[46,47]

Antimicrobial activity

Several papers present the antimicrobial activity of plant extracts, including fruits such as lemon, orange and pineapple.^[51] Studies using pineapple peels, the activities against pathogenic bacterial strains were verified, by the agar diffusion test against pathogenic bacterial strains (*Klebsiella pneumoniae* K2044, *Pseudomonas aeruginosa* MTCC4676, *Bacillus subtilis* Py79 and *Xanthomonas axonopodis* pv. *Malvacearum* LMG859). It showed that methanolic extract of *A. comosus* peels can act as antimicrobial agent, but appropriate studies with adequate safety information should be performed.^[52]

Another study showed that the aqueous extract of *A. comosus* crown leaves showed proteolytic, gelatinolytic, collagenase, fibrinolytic activity, considerable antibacterial and antifungal activities. Collectively, these properties have revealed their application for treatment of microbial infection and as a healing agent.^[53] Nanoparticles obtained with *A. comosus* extract and pineapple leaf extract proved to demonstrate antimicrobial properties.^[54]

Antioxidant activity

Ananas comosus is the most processed tropical fruit generating large amounts of residues, 25-35% are residues with high content of compounds with antioxidant activity, which gives them a huge industrial potential (WU, 2012). The total phenolics, flavonoids and antioxidant activity of *A. comosus* fruits, identified the presence of phenolic compounds, and the antioxidant activity of the extract according to the amount present in the fruit extract, rich in phenolic compounds that provides a good source of antioxidant.^[55]

In order to verify the antioxidant capacity of various tropical fruits using the DPPH method, it was observed that the *A. comosus* extract showed moderate action between 60-70% scavenged of the DPPH radical.^[56] The

β -carotene oxidation technique reveals a modest value for pineapple residue (47.66%).^[98] The concentration of phenolic compounds from pineapple fruit pulp residues showed values of 0.0860 \pm 0.0145 g de AGE. 100 g⁻¹ in aqueous extract and 0.0911 \pm 0.0099 g of AGE 100 g⁻¹ in hydroalcoholic extract.^[57] On the other hand, performing the same study on three cultivars of *A. comosus*, others researchers observed much higher values around 0.30 \pm 0.003 to 0.492 \pm 0.4 g of AGE. 100 g⁻¹ for 70 % methanolic extract.^[58]

In the quantification of flavonoids in pineapple fruit puree, values for the total flavonoid content of 0.0867 g QE 100 g⁻¹. Studying three extracts (ethyl acetate, methanol and water) of the pineapple fruit observed that flavonoid contents ranged from 0.394 to 0.552 g QE g⁻¹ of weight, while for phenolic content were from 0.026 to 0.561g QE g⁻¹ of weight.^[59] In the same study, the authors evaluated the total phenolics, flavonoids and antioxidant activity of pineapple fruits, and found that the extent of the antioxidant activity of the extract is in accordance with the amounts of phenolic compounds present in the rich pineapple fruit extract in these compounds, which provides a good source of antioxidant.^[55]

Other ethnobotanical studies report the use of *A. comosus* as antioxidant, thus correlating the presence of phenolics and flavonoids as the main substances that can express this activity. The antioxidant capacity of aqueous and hydroalcoholic extracts of pineapple pulp residues, using the DPPH free radical was evaluated. It was found EC₅₀ of 7486.5 μ g mL⁻¹ and 3293.92 μ g mL⁻¹, respectively.^[57] In the analysis of leaves of different Bromeliaceae's species, found EC₅₀ of 64.24 μ g mL⁻¹ to the methanolic extract of *A. comosus* var. *bracteatus*.^[97]

Different studies have evaluated the presence of antimalarial activity of natural substances from plants and *A. comosus* is indicated.^[60,61] However, research indicates that *A. comosus* presented weak activities because its IC₅₀ (> 100 μ g mL⁻¹). The report of antimalarial activities was supported by the *in vivo* study of this plant against *Plasmodium berghei* in mice. This same study suggests that *A. comosus* may be an immune stimulant, thus relieving the symptoms of the disease.^[62]

Activity against rheumatoid arthritis

Studies indicate bromelain activity against rheumatoid arthritis (RA), with specific inhibitory activities on Cox-2 and PGE2.^[63] The methanolic extract from *A. comosus* peel exhibited antirheumatic activity increasing the levels of SOD, CAT, and GPx enzymes in the liver, kidney, and spleen, thus decreasing CRP and prostaglandin PGE2 levels in the serum of arthritic rats. In addition, that paw histopathology also showed a reduction in necrosis when treated with the extract, flavonoids and tannins present in the extract may be responsible for the observed activity. The same author reports that the production of PGE2 by the rheumatoid synovial tissue causes cartilage erosion and the decrease of PGE2 levels when administered with the tested extract indicates the anti-inflammatory potential of *A. comosus*. In addition, it also suggests the possible use of *A. comosus* to protect cartilage from damage caused during RA.^[64]

Cardiovascular protective effects

Research also links the use of *A. comosus* with cardiovascular protective effects. A study using rats to assess the protective effect on isoproterenol-induced structural and myocardial damage found that *A. comosus* hydroalcoholic extract protected the myocardium from damage, maintaining cell membrane integrity and improving cardiac systolic / diastolic dysfunction induced by isoproterenol. Pretreatment with 200 mg kg⁻¹ extract showed decreased area of infarction with coagulative necrosis and inflammatory cells with moderate myocardial edema, there was mild edema. However, there was no infarction and inflammatory cells and cardiac fibers were within normal limits in the myocardium of

rats pretreated with the extract. The protection may have been mediated by *A. comosus*-induced increase of antioxidant activities in myocardial enzyme, concluding that *A. comosus* has strong activity due to the presence of bromelain and other antioxidant substances.^[65]

To evaluate cardioprotection, the potency of pineapple anti-inflammatory activity in the necrotic myocardium in combination with the losartan angiotensin blocker. Sprague-Dawley rats were tested using losartan (LTN) (30mg kg⁻¹, 10 days, VO), and pineapple doses (100, 250 and 500 mg kg⁻¹, 30 days, VO) and subsequently subjected to isoprenaline administration (150 mg kg⁻¹). Subsequently, histopathological observations and biochemical tests were performed to evaluate antioxidant activity. The elevated LDH and CK-MB in cardiac tissue and the enzymes SOD and catalase increased significantly, thus proving the efficacy of cardiac protection of *A. comosus*. The authors attributed the efficacy to the presence of bromelain, which is responsible for the increase of biomarkers and the association with the drug.^[66]

Hypolipidemic and hypoglycemic activity

Among the plant species that present hypolipidemic and hypoglycemic activity, there are several ethnobotanical reports and research showing that *A. comosus* presents the pharmacological activities mentioned. According to Table 1, the following papers present research related to hypolipidemic and glyceic activity and mostly report the presence of phenolic compounds as the main agents of such activities.^[67-69,71,72,70,73-78]

Different cereals made using the aqueous extract of *A. comosus* fruits were studied, showing that with the use of such cereals *in vivo* hypolipidemic effects were observed, however further research should be conducted with greater numbers of participants.^[72] The hypolipidemic activity was investigated in fructose-fed rats. The study showed that using a dose of 0.40 g kg⁻¹ *Ananas comosus* the serum triglycerides significantly reduced by 40% in rats. Since the animals' diet was increased, serum cholesterol levels increased and remained high within 7 days after the removal of high fat diets, by the administration of *A. comosus*, demonstrating the hypolipidemic activity of the species in question.^[73]

Ananas comosus could be a new alternative drug of plant origin for the treatment of hyperlipidemia, and its activity occurs by inhibition of HMG-CoA reductase and activation of LPL. The mechanism for hypolipidemic action of *A. comosus*, where it reports that the phenolic compounds present in *A. comosus* leaves act on hepatic fat metabolism, his results showed that the phenolic compounds called PLP, by the author, significantly decreased the abdominal load and the liposide accumulation in the diet. Its mechanism is different from fibrates, but somewhat similar to statins, being a good adjunct to fibrates in the treatment of hyperlipidemia. Due to the protein level, PLP increased the expression of carnitine palmitoyltransferase 1. Regarding mRNA expression, PLP mainly promoted CPT-1, PGC1a, UCP-1 and AMPK expression in mitochondria, PLP appeared to increase fat metabolism in mitochondria. Since the *p*-coumaric acid, a major component of the PLP, collaborated with their activity. In addition, phenolic compounds and *p*-coumaric acid have strong antioxidant properties, enhancing safety at preliminary values. However, further research is still important to investigate the effects of phenolic compounds and the *p*-coumaric acid precursor.^[77]

Hypoglycemic activity

The hypoglycemic activity of *A. comosus* ethanolic extracts of leaves was investigated. The insulin sensitivity in streptozotocine-treated wistar rats fed low-fat high-dose diets and challenged with exogenous human insulin, treatment was used with *A. comosus* at an oral dose of 0.40 g kg⁻¹ and *A. comosus* application was found to inhibit the development of insulin resistance in HepG2 cells. In addition, the authors suggest that

A. comosus may improve insulin sensitivity in type 2 diabetes and be developed as a potential new natural product for the treatment of insulin resistance in diabetic patients.^[69]

To diabetic complications, the leaf extract of *A. comosus* attenuated the increase of triacylglycerol in mice with acute fructose administration indicating inhibition of endogenous triacylglycerol synthesis.^[68] However, in another model that induces hypercholesterolemia, mice treated with the plant had no plasma lipid increase in 24h. Its indicate that *A. comosus* activates the lipase enzyme, besides inhibiting HMG-CoA reductase inhibiting endogenous cholesterol synthesis, being related to hypolipidemic action.^[77]

Anti-hyperlipidemic

The first investigation of anti-hyperlipidemic activity in rats was carried out due to the traditional use. To evaluate the anti hyperlipidemic potential of the hydroalcoholic extract of the *A. comosus* leaves, rats with hyperlipidemic induced by high fat diet was treated with different concentrations of extracts. The amount of fiber present in *A. comosus* is directly responsible to the improvement in insulin and cholesterol levels, through the action of lipids and carbohydrates. As results of the treatment with extract the rats had significant reduction in blood glucose levels and LDL cholesterol, it was found a lipid-lowering effect in cholesterol of 32% and triglycerides of 49% after 56 days of administration.^[79] However, studies that assess the true potential of the species and indicate which substances are responsible for such activities are necessary.

Ananas comosus is widely used in diseases that affect the respiratory system, such as mucolytic and fluidizing secretions and upper airways in home preparations.^[80] Bromelain is a set of enzymes present in *A. comosus*, which have different pharmacological activities, including mucolytic action and there respiratory tract present in several studies.^[81-83]

The use in the treatment of burns

Bromelain, known as an efficient debridement agent in the treatment of burns and tissue regeneration.^[84] If applied topically (35% on a lipid basis) is able to promote complete debridement in experimental burns in rats in about 2 days, in comparison with collagenase, which took about 10 days, with no side effects or damage to the adjacent burnt tissue.^[85]

A recent study evaluated the healing potential of chitosan nanofibers containing bromelain (2% and 4% w / v) in burns induced in rats for 21 days and the results demonstrated that chitosan nanofibers with bromelain (2%) had better physical-chemicals and release profile, in addition to lower cytotoxicity than chitosan nanofibers with 4% bromelain. Compared to pure chitosan nanofiber, chitosan nanofibers with 2% bromelain were more efficient in healing burns, evidencing their wound healing activity and as an effective natural topical treatment for burn healing.^[86]

Treatment of infections

Pineapples are used to help in cure of infections such as bronchitis and sore throat, due to the benefits of bromelain to the respiratory tract are bronchitis, sinusitis, mucus shrinkage, allowing the mucus to drain and relieve facial pressure and headache commonly caused by sinusitis.^[87] Bromelain is a proteolytic and mucolytic enzyme, significant in the dissolution of bronchial secretion, widely used in the treatment of young children diagnosed with acute sinusitis, and safe for use in children.^[82]

The potential of bromelain when associated with others medicines

It is well described that bromelain is capable of increasing the tissue permeability of penicillins and tetracyclines after oral administration.

This promotes increased absorption and leads to improved diffusion after subcutaneous and intramuscular application of antibiotics, culminating in increased serum and tissue levels and reduced side effects.^[88,89]

The association of bromelain and antibiotic therapy of 53 hospitalized patients with pneumonia, bronchitis, staph infections, thrombophlebitis, pyelonephritis and rectal abscesses. In all disease states, there was a significant reduction in morbidity compared to antibiotics alone. In addition, among the 53 patients, 23 were unsuccessful on antibiotics, however, 22 of them responded favorably to the combined treatment of bromelain and antibiotics.^[90] In a double-blind clinical study on acute sinusitis of the patients who received bromelain, 83% had complete resolution of nasal mucosa inflammation versus 52% in the placebo group.^[91]

This review of the works published from 1966 to 2019 involving pharmacological actions of *A. comosus* relates the medicinal potential of the species and showed that *A. comosus* is used in popular practice in different countries, mainly Asian and African continents, in South America. Brazil has the largest number of publications. This study demonstrated that the species in question is the focus of *in vitro* and *in vivo* scientific research for several pharmacological actions, besides presenting pharmacologically important substances and secondary metabolites, especially phenolic compounds, mainly phenolic acids and flavonoids, as well as steroids and bromelain. Such compounds have different potential biological activities was already been investigated in studies.

However, there is a need for work to confirm its pharmacological potential, establishing the safe use as well as the identification of other active substances. In addition, the fruit and vegetable industry generate a large number of wastes, which can serve as a basis for the extraction of these commercially important substances.

The results of this work should stimulate the continuity of studies with this species and its varieties, since the popular use of vegetables directs scientific research to search for new therapies. The multidisciplinary studies involving phytochemicals and pharmacologists are becoming increasingly important in defining the therapeutic and toxic potentials of *A. comosus*.

CONCLUSION

Several research groups have been working with plant species due to the interest in the scientific confirmation and validation of the effect of medicinal plants used in folk medicine. *Ananas comosus* presents satisfactory results in several researches involving biological / pharmacological activities, making this species attractive for future research, requiring further studies that prove mechanism of action and establish safe conditions for use.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACHe: Acetylcholinesterase Enzyme; **ALT:** Alanine Transaminase; **AMPK:** Adenosine 5'-monophosphate (AMP)-activated protein kinase;

AST: Aspartate Transaminase; **CK-MB:** Creatine kinase-MB; **CPT-1:** Carnitine palmitoyltransferase 1; **EDTA:** Ethylenediaminetetraacetic acid; **HMG-CoA reductase:** 3-hydroxy-3-ethylglutaryl-CoA reductase; **IC₅₀:** Half-Maximal Inhibitory Concentration; **LC₅₀:** Lethal Concentration; **LDH:** Lactate Dehydrogenase; **LDL cholesterol:** Low-density lipoprotein cholesterol; **PGC1α:** Peroxisomal proliferator-activated receptor gamma coactivator alpha; **PLP:** Pineapple leaf phenols; **SOD:** Superoxide dismutase; **TG:** Triglycerides; **UCP-1:** Uncoupling protein 1.

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