Pharmacological Actions of *Ananas comosus* L. Merril: 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 synthesize 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 actions 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 phytotherapics has occurred since ancient times, it is essential to carry out research identifying 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.[3] Brazil has an invaluable source of natural resources to obtain drugs, although the pharmacological potential of our native species have been poorly studied.[4]

In Brazilian territory, Bromeliaceae’s family is very common. It’s include approximately 78 genera and about 3663 species, which are divided into subfamilies: Pitcairnioideae, Bromelioideae, Tillandsioideae, Brocchinioideae, Hechtioideae, Lindmanioidae, 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, its 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, antiadibetic and others. In addition to reports of bromelain enzyme and cysteine proteases, various special secondary metabolites as triterpene, steroids, flavonoids, glycerols, cinnamic acid derivatives, among others, were reported.[7-10]

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 actions in *A.comus* 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 varieties, described in the literature. It has expected that this review...
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, antihelmintic; antimicrobial; antioxydant; antilutetrophic; 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 ethnomedical 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, antilutetrophic and antioxydant**

Studies assessing the ability of *A. comosus* to terminate pregnancy are old, evaluated the isolated substances ergosterol peroxide, β-sitosterol, 5-estigmastene-3β,7α-diol, 5α-stigmastane-3β, 5,6β-triol, 3 monobenzoate from pineapple leaf extracts and also they identified that when administered in rats it showed abortifacient enzyme. The compounds: ergosterol peroxide, β-sitosterol, 5-estigmastene-3β,7α-diol, 5 stigmastene-3p-7p-diol, 7-oxo-5-stigmastene-3p-ol, 5a Stigmastane-3β, 5, 6β- 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. 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. 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.

According to studies conducted in rats and rabbits steroid 5α-stigmastane-3β, 5,6β-triol 3-monobenzoate also exhibit antilutetrophic and antioxydant 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 F2α, acetylcholine and KCl. Furthermore, the authors concluded that the extract acted by multiple mechanisms as antagonism of Ca\(^{2+}\) type L channels, interfering in intracellular Ca\(^{2+}\) release mechanism, and releasing nitric oxide, characterize the extract as a promising candidate to be developed as a tocolytic agent.

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.

**Anti acetylcholinesterase**

Different studies report that plant extracts have inhibitory activity of the acetylcholinesterase enzyme (AChE). An *in vitro* study using extracts of fruits from *A. comosus*, showed that only the aqueous extract showed 4.3% inhibition, it is considered low activity if evaluated according to Vinhuta et al. 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. 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.

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. 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. 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. 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 a antitumor, and indicate that the bromelain presence in *A. comosus* as the main agent of such activity. 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.
cytotoxic activity of \(A.\ comosus\) pulp and peel was verified with \(Aq.\ salina\), its showed \(LC_{50}\) 25 \(\mu\)g.mL\(^{-1}\) and 29.6 \(\mu\)g.mL\(^{-1}\), respectively. 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 \(\mu\)g.mL\(^{-1}\); moderate to 100 to 500 \(\mu\)g.mL\(^{-1}\) and high to \(LC_{50}\) below 100 \(\mu\)g.mL\(^{-1}\).

### Anticoagulant
The availability of \(A.\ comosus\) and the various activities of bromelain had led to the evaluation of this enzyme as anticoagulant. 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.

### 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.[40]

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, naringen, 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.[40] On the other hand, the species in question evaluated against the Rhizaphalus microplus parasite and the Haemonculus contortus helmitch, regarding the parasite, showed activity and with respect to helmitch 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. Malvaearum LMG859). 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 antiinflammatory 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 glycemic 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\(^{-1}\) A. 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 streptozotocin-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.\[81-84\]

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.\[88\]

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.\cite{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.\cite{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.\cite{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 research, requiring further studies that prove mechanism of action and presents satisfactory results in several research involving biological and pharmacological actions and pharmacologists are becoming involved directly 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; AIT: 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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