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Bioactive potentialities of *Grewia flavescens* root extract in the treatment of alcohol dependence: Preliminary phytochemical study

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Abstract

Although the use of plants for medicinal purposes is an ancient practice, there is a perception that in the field of chemical dependency, its role has been and is little studied. With regard to alcohol dependence, the third leading cause of hospitalization in psychiatric hospitals in Mozambique, an ethnobotanical work was carried out in 2018 in the Municipality of Massinga, province of Inhambane, with the aim of identifying with practitioners of traditional medicine, the plants they use in their treatment, having resulted, among other plants, in the identification of *Grewia flavescens*, from which the need arose, based on phytochemical prospecting and literary framework support, to carry out a study of a preliminary nature on the bioactive potential of the root extract (part indicated in the survey) of *Grewia flavescens* in the treatment of alcohol dependence. The results showed the presence of Flavonoids, Tannins, Alkaloids, Triterpenoids and Saponins. About this group of bioactives, there is bibliographical evidence that points to the anxiolytic and anti-depressant action of Flavonoids, Saponins and Alkaloids, allowing to infer that these can act as mood stabilizers in patients in the phase of alcohol withdrawal syndrome and craving during treatment, not despite deepening from preclinical studies.

Keywords: *Potentialities, Bioactives, Grewia flavescens, dependence, alcoholic*

Introduction

The use of plants for medicinal purposes is a remote practice [1] that emerged from the human capacity to learn from the challenges of the environment. Regarding its role in medicine, it appears that even with advances in this field, there are still countries, mainly in Africa, where a considerable part of the population depends on plants to deal with health problems [2].

In the particular case of Mozambique, despite the country hosting a large repository of plants, [3] refer that only 15% of this source is used in the treatment of diseases, a fact that demonstrates that there is much to be explored, and because of this it has deserved the attention of researchers in the area in this country, despite, if you notice that the interest in its potential in the field of mental health has not yet evolved, it can be said that it is in the embryonic phase.

Therefore, it is in this context that a survey was carried out in Mozambique, in the municipal town of Massinga, in 2018, on plants that are used by practitioners of traditional medicine (PMT) in the treatment of alcohol dependence, a disorder that in this country, according to the Ministry of Health (MISAU) is the third leading cause of admission to psychiatric hospitals [4], resulting in the identification of six plant species, including *Grewia flavescens*.

Grewia flavescens is a plant from the semi-arid and sub-humid tropical zones of Africa, Saudi Arabia, Yemen and India used to treat organic and infectious diseases [5]. Focusing on the medicinal value of this plant, [6] highlight the anti-ulcer activity and point out its role in the treatment of colic, wounds, cholera, dysentery, and as an anthelmintic. In the traditional

Indian healthcare system, it is considered a central nervous system (CNS) anti-depressant, anti-inflammatory, antimalarial, antidiabetic and analgesic [7].

There was no reported evidence regarding its role in the treatment of alcohol dependence, however, the present study departed from the principle that the potential of this plant depends on the presence of bioactives that have a similar action to the conventional drugs used for this purpose. Therefore, the objective of this research was based on the results of the preliminary phytochemical prospection and bibliographical support, to analyze the possibility of the extract of the root of *Grewia flavescens*, partly indicated by the PMTs, being a candidate for phototherapy in this field.

Materials and methods

Data collection was based on preliminary phytochemical prospecting to identify the compounds present in the *Grewia flavescens* root extracts and on bibliographical consultation to seek a possible relationship between the substances identified in the extract and the treatment of alcohol dependence.

Materials

The materials used in the preliminary phytochemical prospecting were:

➔ DENVER INSTRUMENT XL-610 brand analytical balance (e=0.01g)

➔ Erlmayer flask

➔ Greenhouse

➔ Shake-O-mat mechanical shaker (Labotec)

➔ Rotary steamer

➔ Soxhlet apparatus

➔ Water bath

➔ funnel

➔ Volumetric flask

➔ Filter paper

➔ test tube

➔ Dropper

➔ Graduated cylinder

➔ electric stove

➔ Pipettes

➔ Reagents

➔ *Grewia flavescens* root

Methods

Preliminary phytochemical prospecting

Preliminary phytochemical prospecting was carried out in the research and extension laboratory of the chemistry department of the Eduardo Mondlane University (UEM), and was carried out by means of two groups of procedures, those for obtaining the extracts (cold maceration and Soxhlet), and those for identifying the substances present in the *Grewia flavescens* root extract (coloring and precipitation reactions).

Obtaining extracts

Obtaining *Grewia flavescens* root extracts, essential for the compound identification reactions, was carried out through cold maceration and Soxhlet extraction, the procedures are described in the works of [8, 3]. The solvent used was 96% ethanol.

Cold maceration

Using a DENVER INSTRUMENT XL-610 analytical balance (e=0.01g), approximately 17.73 g of the *Grewia flavescens* root dried in an oven were weighed. Then, the weighed material was placed in the Erlmayer flask and 300 mL of the solvent (ethanol) was added to it so that it was submerged. Subsequently, this material was taken to a Shake-O-mat mechanical shaker (Labotec) for 24 hours at a speed of 144 units. To reduce the solvent of the obtained solution, this was taken to a rotary evaporator in order to concentrate it, and using a funnel, a volumetric flask and filter paper, it was filtered. The volume obtained was ignored due to the fact that the research was qualitative.

Soxhlet Extraction

The steps of weighing the material, filtering and concentrating the obtained solution are similar to those of maceration. The material obtained from weighing was introduced into the Soxhlet apparatus, where it remained for 3 hours for extraction.

Identification of compounds present in Grewia flavescens root extract

The identification of the compounds present in the *Grewia flavescens* root extract was carried out by means of colorimetry and precipitation reactions. Here, attention was given to the classes of secondary metabolism substances, for which material conditions were available (existence of reagents) for their identification, in this case, Flavonoids, Tannins, Alkaloids, Saponins, Steroids, Triterpenes, Anthraquinones, and Phenols. The procedures used are those recommended by [9, 10, 11, 3, 12, 13].

The presence of these groups in the *Grewia flavescens* root extract was checked according to the

criterion used by [9], according to which the observation of the expected characteristic reaction indicates the presence of the result.

Colorimetry and precipitation reactions

Characterization of Flavonoids

For the identification of Flavonoids, 3mL of *Grewia flavescens* root extract were introduced into a test tube. Then, 1 mL of concentrated hydrochloric acid (HCl) and then 1 cm of magnesium tape (Mg) were added to the test tube, and the result was observed.

Characterization of Tannins

Three drops of iron (III) chloride alcoholic solution ($FeCl_3$) were added to 3 mL of *Grewia flavescens* root extract contained in a test tube, shaken, and observed.

Characterization of Alkaloids

2 mL of HCl (10%) was added to 3 mL of the *Grewia flavescens* root extract solution, the mixture was heated for 10 minutes at a temperature of 50°C, and after cooling, the Drangendoff reagent was added, and observed.

Characterization of Saponins

5 mL of ethanolic extract of *Grewia flavescens* root was diluted in 10 mL of distilled water in a test tube, stirred for 15 minutes, and possible alterations were observed.

Characterization of Steroids/Triterpenoids

Two tests were carried out, the Libermann-Burchard test to identify Steroids/Triterpenoids, and the Salkowski test to confirm the presence of Triterpenoids.

Libermann-Burchard Test (Steroids): To the extract of *Grewia flavescens* root treated with Chloroform ($CHCl_3$) and filtered, drops of Acetic Anhydride ($C_4H_6O_3$) were added, and stirred. Subsequently, making it drain along the walls of the tube, 1 mL of concentrated sulfuric acid was added, and observed.

Salkowski test (Triterpenes): To the extract of *Grewia flavescens* root treated with $CHCl_3$ and filtered, drops of concentrated sulfuric acid (H_2SO_4) were added, stirred and left to stand.

Characterization of Anthraquinones

10 mL of ethyl ether ($C_4H_{10}O$) was added to 5 mL of *Grewia flavescens* root extract, then 2 mL of ammonium hydroxide solution (NH_4OH) was added, stirred and observed.

Characterization of Phenols

Three drops of the $FeCl_3$ solution were added to 3 mL of the ethanolic extract of the *Grewia flavescens* root contained in a test tube, it was shaken and observed.

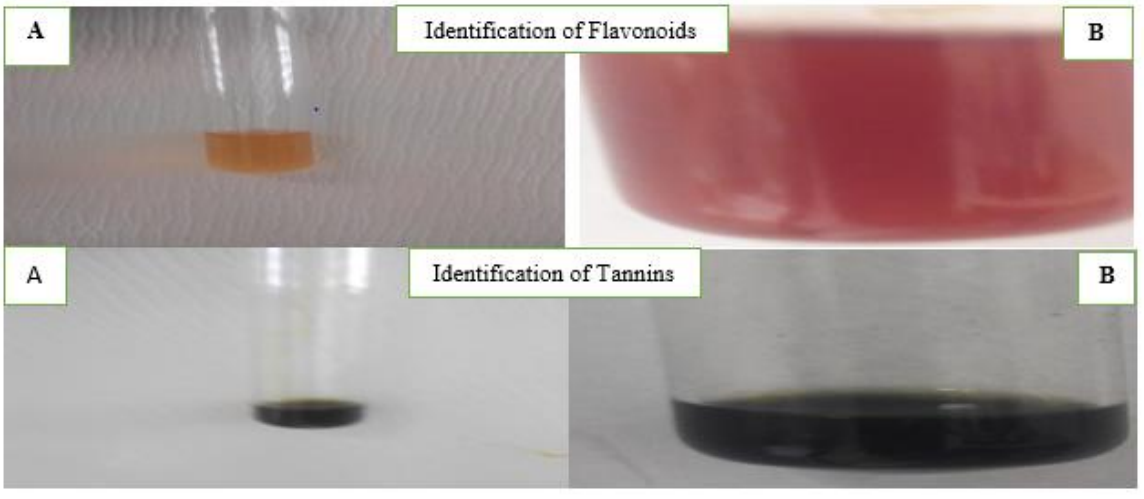
Bibliographic consultation

The bibliographic consultation was carried out in accordance with [14], and comprised: First, the consultation of materials that dealt with the medicinal role of *Grewia flavescens*, second the consultation of bibliographies that deal with the medicinal role of the identified compounds, above all, in the possibility of treating chemical and alcoholic dependency. The lack of printed bibliographic works dealing with these themes limited the search to online platforms, with emphasis on repositories of academic works and electronic journals.

Results and discussion

Results

Phytochemical tests performed with *Grewia flavescens* root extracts resulted in a change in color and/or the presence of precipitates at the bottom of the solutions obtained, as can be seen in Figure 1.



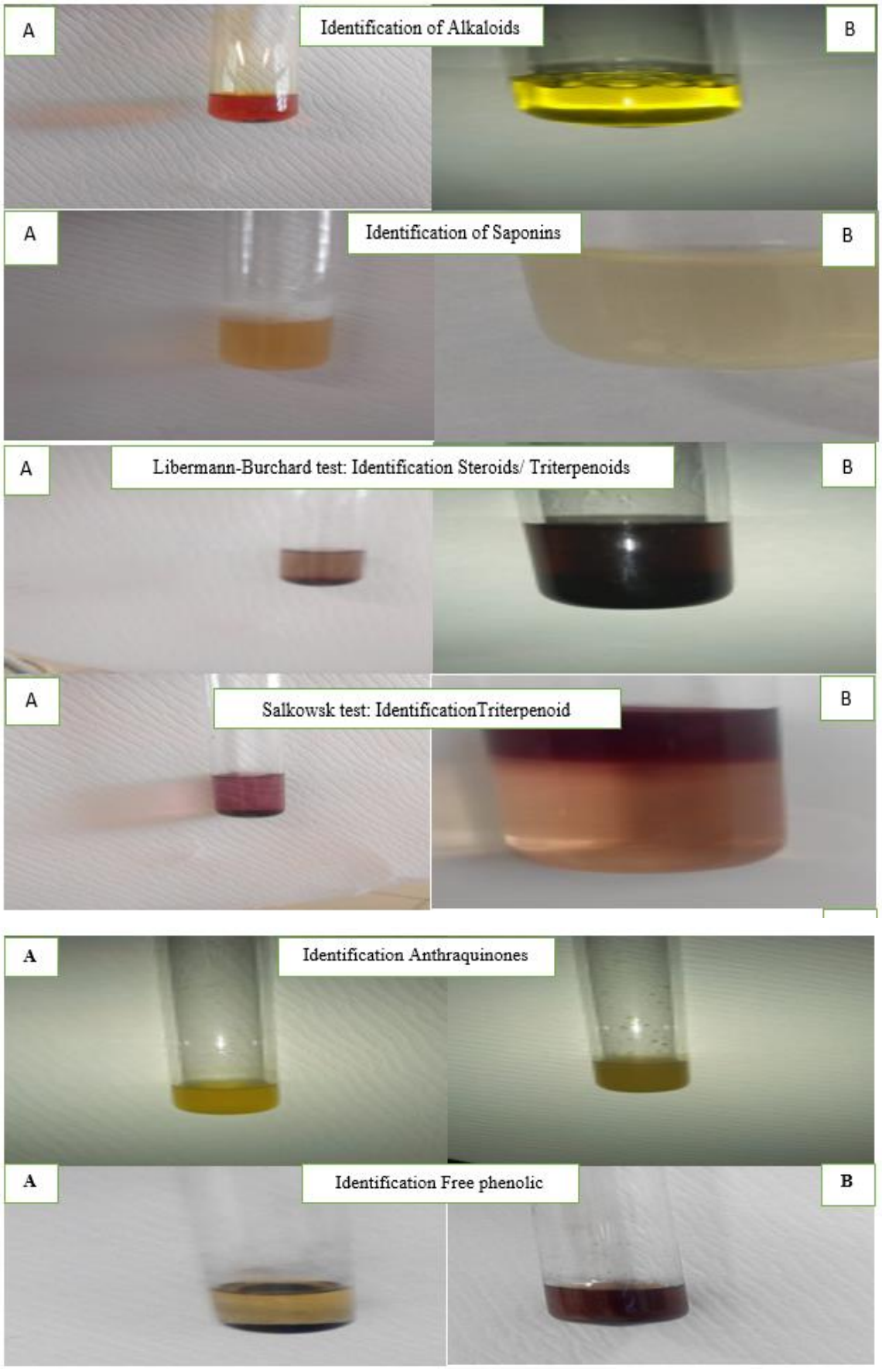


Fig 1. Ethanol extract **A** (Maceration) and **B** (Soxhlet). **Source**: Authors (2023)

The meaning of the final hue of the solutions and the precipitates formed after the phytochemical tests are shown in table 1.

Table 1. Group of phytochemicals present in *Grewia flavescens* root extracts.

Compounds	Results				Bibliographic support
	Characteristic of the solution (shade/precipitation)		Interpretation		
	Maceration	Soxhlet	Maceration	Soxhlet	
Flavonoids	Orange solution with a reddish ring on the surface	rosy red solution	Slightly+	+	[9, 13, 15]
Tannins	loaded green solution	loaded green solution	+	+	[13, 12]
Alkaloids	Red solution with dark precipitates in the background	Light yellow solution with dark precipitate	+	+	[16, 15]
Steroids/ Triterpenoids (Liebermann-Burchard test)	brown red solution	Red-brown solution on the surface	-	-	[9, 12, 17, 15]
Triterpenoids (Salkowski test)	brown red solution	The red-brown solution in the upper phase	+	+	[17, 15]
Saponins	Solution with a persistent foamy ring on the surface	non-foaming solution	+	-	[9, 18, 13]
Anthraquinone	yellow solution	yellow solution	-	-	[16, 18, 19, 8]
Free phenolic compounds	Light brown solution with dark precipitates	brown solution with dark precipitates	-	-	[3, 15, 9]

Positive (+); Negative (-). Source: Authors (2023)

According to Table 1, the preliminary phytochemical prospection of the *Grewia flavescens* root extract confirmed the presence of Flavonoids, Tannins, Alkaloids, Triterpenoids, and Saponins, except for Steroids, Anthraquinones, and Free Phenols, since the tests for their identification showed different results than expected.

Although the presence of Steroids in the *Grewia flavescens* root extract has not been confirmed, [20] refers to their existence in this plant.

Discussion

[21, 22, 23, 24] point out that conventional products commonly used in the treatment of chemical dependency act as an aversive, anticonvulsant, antidepressant, anxiolytic, mood stabilizer, anti-psychotics, and beta blockers. [23] advance that the administration of these products is done in the main stages of alcohol dependence, namely, alcohol withdrawal syndrome (AAS) (phase where the total or partial interruption of alcohol use by the dependent causes hyper-excitability of the central nervous system), alcohol tolerance (phase where the usual amount of the drug does not cause the user the effects he seeks, and to obtain them higher doses are needed) and craving (phase where there is an intense desire to consume the substance).

Therefore, the reflection made in this work was based on the understanding that in order to promote the desired effect in the treatment of alcoholic dependence, the secondary metabolism classes identified in the *Grewia flavescens* root extract must have these properties and act in the main stages of dependence. alcoholic.

Flavonoids and alcohol dependence

In the field of pharmaceutical research, specifically in the search for natural products with the potential to treat alcohol dependence, promising results were found in relation to the role of Flavonoids. Studies cited by [25] revealed that extracts of Kudzu (*Pueraria lobata*) containing a variety of isoflavones, and species of flavonoids, reduced alcohol consumption

in rats and hamsters. Explaining the mechanism of action of isoflavones, [26] pointed out that research has shown that they are inhibitors of the enzyme aldehyde dehydrogenase (ALDH2), responsible for eliminating the acetaldehyde that results from the metabolism of ethanol in alcoholic beverages, which is at the origin of stress after alcohol consumption and can therefore act as aversives.

Despite the existence of this evidence surrounding the action of flavonoids as aversive in the treatment of alcohol dependence, it is understood that in this regard, the results found in the present research are not conclusive, since the identification of this class of compounds using the Schinoda test did not confirm the presence or absence of isoflavones (associated with the aversive role), since, according to [27], in this type of test, they do not develop a reaction.

In another study, [28] highlighted the role of Dihydromyricetin, a Flavonoid component of herbal medicines, in counteracting acute alcohol intoxication and reducing its consumption in the context of intermittent voluntary intake in rats. [29] when reflecting on the phytotherapy of alcoholism, pointed out several species of flavonoids with studied mechanisms, highlighting the isoflavones Daidzin (*Pueraria lobata*), the Flavonoids hovenodulinol (*Hovenia dulcis*), the Flavonolignin complex (*Silybum marianum*), the Benzoflavones (*Passiflora incarnate*), and Flavonoid polyphenolic compounds (Propolis).

This variety of flavonoids with evidence in the treatment of alcohol dependence reinforces the idea that more species of this class may have similar effects, a hypothesis that in the case of the present research can only be proven in later stages (*in vitro* or *in vivo*).

Still on the treatment of alcoholism, study cited by [30] report that this condition is often associated with psychiatric comorbidities such as depression and anxiety disorder and can be classified as a triggering factor or a condition of coexistence, in which one reinforces the other when not treated properly. Thus, in the case of anxiety, [31] emphasizes that the class of natural compounds that has shown great potential in the search for new molecules with anxiolytic activity are Flavonoids, a fact reinforced by [32, 33, 28]. It is believed that, like conventional medications, they act in the SAA and fissure phase, periods in which anxiety disorders are observed.

Regarding the antidepressant action of flavonoids, note that this is reported in the works of [34]. This author reported the antidepressant activity of Rutin, a Flavonoid, in rats and through co-administration experiments with Serotonin and Noradrenaline inhibitors. According to [34], several studies that show the antidepressant role of Flavonoids have been published, and recently we can cite those of [35, 36, 37].

Therefore, in the treatment of alcohol dependence, the evidence found shows that the possibility of the Flavonoids identified in the present study acting as anxiolytics and antidepressants is greater than as aversives, given the variety of compounds in this group that present these activities.

Tannins and alcohol addiction

No studies were found that relate this compound to an action that can be associated with the treatment of alcohol dependence.

Alkaloids and alcohol dependence

Although little has been found about it, the Alkaloids have been related to anticompulsive action in the treatment of addiction. [38] reported that ibogaine, a kind of Alkaloid, has been used for its anticompulsive effect, acting on the dopaminergic and serotonergic systems. In turn, studies cited by [39] refer to the occurrence of ß-carbolines in *Cipó banisteriopsiscaapi*, and dimethyltryptamine (DMT) in Psychotriaviridis leaves that act on the serotonergic level with a similar effect. Regarding ß-carbolines, [40] adds that they can act as anxiolytics. In the same vein, [41] when studying hydroalcoholic extracts of *Erythrina mulungu* flowers, confirmed that other species of alkaloids such as 11-hydroxyerythravine, erythravine and alpha-hydroxyerysothrine may also have anxiolytic effects, data that corroborate those found by [42] when they studied the same plant.

In another aspect, [43] gathered scientific evidence indicating 37 alkaloids derived from L-tryptophan (1) as potential therapeutic candidates for the treatment of depressive disorders. Although not conclusive, the data presented here suggest that the presence of alkaloids in *Grewia flavescens* root extracts potentiate it to present anxiolytic and antidepressant properties in the treatment of alcohol dependence. However, despite these records, it is understood that there is a need to advance to pre-clinical studies in order to confirm whether the *Grewia flavescens* extract has species of alkaloids that, like those reported, have similar activities.

Triterpenoids and alcohol dependence

Reports by [44] associate the anxiolytic action of Ginsenosides with the triterpene Saponins found in *Panax ginseng C. A. Meyer* (Araliaceae). whether the hypothesis is isolated evidence or means that triterpenoids are understudied in this field.

Saponins and alcohol addiction

In this regard, studies cited by [44] report that studies using animal models of anxiety indicated that *P. ginseng* has anxiolytic activity probably related to the presence of Saponins. Still in this context, [31] refers that anxiolytic action was verified in the Saponins of *P. quinquefolium* in three animal models and cite one study to mention that the action of this group of compounds on the GABAergic system had already been demonstrated, which may explain, in part, the anxiolytic effect observed. [45] found in the experiment carried out with the extract of the Suanzaorenhehuan formula (SHF) used to treat depression-like disorders in China that the Saponin part of the extract acted effectively as an antidepressant. These data suggest that compounds in this class may act as anxiolytics and antidepressants.

Conclusion

The results of the phytochemical prospection carried out on the Grewia flavescens root extract show the presence of Flavonoids, Tannins, Alkaloids, Triterpenoids, and Saponins.

There is experimental evidence in the bibliographic field that points to the antidepressant and anxiolytic actions of Flavonoids, Alkaloids and Saponins that make these compounds act as mood stabilizers in patients in the AAS and fissure phase in the treatment of alcohol dependence.

Regarding tannins, the present study did not find evidence relating them to the treatment of alcohol dependence.

Although the *Grewia flavescens* root extract can be associated with antidepressant and anxiolytic action, two important properties in the treatment of alcohol dependence in the stages of AAS and fissure, this research is not conclusive as to its effectiveness, requiring deepening from preclinical studies.

Authors' contribution

Elvino José de Sousa Ferrão and Edilson Armando de Germano Janeque designed and carried out the ethnobotanical survey of plants that are used by practitioners of traditional medicine in the municipal town of Massinga in the province of Inhambane in Mozambique, which culminated in the study reported in this manuscript. The first and second authors elaborated the phytochemical prospecting protocol, carried out the chemical analyzes and wrote the final report that originated this article.

Declaration of conflict of interest

Nothing to declare

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