

Review of Efficacy and Safety Evidences of Ethiopian Medicinal Plants Traditionally Used For the Treatment of Rabies

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Abstract

Background: Where rabies vaccines are physical inaccessible and economically unaffordable, traditional medicinal plants are options for rabies management in different parts of Ethiopia. However, most of these plants have not been scientifically investigated.

Objective: This review aims to provide an up-to-date overview of the safety and efficacy data of medicinal plants used traditionally for the management of rabies in Ethiopia.

Methods: A website-based search strategy was employed. Databases (PubMed, Science Direct, Web of Science and Google Scholar) have been thoroughly sought. The search items used were "Rabies in Ethiopia", "Traditional medicinal plants", and "Safety and Efficacy".

Results: The current review revealed that about 80 plant species which belong to 43 families and 68 genera were found to be used in the traditional treatment of rabies in Ethiopia. Among these, only 5 plant species (*Phytolacca dodecandra*, *Justica schimperiana*, *Salix subserrata*, *Croton macrostachyus* and *Silene macroselen*) were scientifically tested in animal models and/or in animal cell lines.

Conclusion and recommendation: According to this review, various medicinal plants have been used in treatment of rabies in Ethiopia on basis of traditional uses. However, there is limited scientific evidence to establish the safety and efficacy of these medicinal plants. More studies with adequate methodological quality in order to investigate the efficacy and safety of those traditional medicinal plants are needed.

Keywords: Efficacy; Medicinal plants; Rabies; Safety

RABV to humans through inhalation and organ transplantation such as corneal transplant from an infected donor has also been suggested [2]. No successful cure for Rabies has yet been found, by the time the symptoms appear, it is generally too late to save the patient. The only way to prevent death is the rabies post-exposure prophylaxis (PEP), which is a serial vaccination against rabies starting as soon as possible after the patient, was bitten by a suspected rabid animal [3]. The correct application of inactivated tissue culture-derived vaccines is highly effective at preventing the development of rabies, and very few failures are recorded. Sheep brain derived Fermi type rabies vaccine is still being manufactured at the Ethiopian Health and Nutrition Research Institute and utilized for the majority of exposed patients in Ethiopia (Birhanu, 2013). It has been a common practice to provide post-exposure vaccines to humans bitten by dogs irrespective of their rabies status. This increases the risk of complications associated with the Fermi type vaccines, as this vaccine accounts for 88% of the vaccines used throughout [4].

In Ethiopia people have no clear understanding on the danger of rabies and believe to cure with different traditional and religious treatment rather than seeking effective post exposure prophylaxis. Eighty percent of the Ethiopian people depend on traditional medicine for their health care (Dawit and Ahadu, 1993), and more than 95% of traditional medicinal preparations in Ethiopia are made from plant origin. Numerous plant species are used to treat diseases of infectious origin like, rabies (Dawit, 1986). The wide spread use of traditional medicine among both urban and rural population in Ethiopia could be attributed to cultural acceptability, efficacy against certain type of diseases, physical accessibility and economic affordability as compared to modern medicine [5]. Various traditional antirabies folk drugs were reported which were used for the treatment of rabies in both humans and animal. In different ethnic groups of the country, about twelve traditional plants were reported by different investigators for the treatment of rabies in animals and humans [6]. Scientific approach needs to be applied towards the safety and efficacy of traditional plants in managing rabies. The main aim of this review is therefore, to show and document the pharmacological and toxicological status of medicinal plants traditionally used for the treatment of rabies in Ethiopia up to 2021 from published scientific studies.

Introduction

Even though rabies has been preventable by vaccination since the 19th century, it still causes more human deaths than any other zoonotic disease [1]. Rabies is a virus that is usually spread by the bite or scratch of rabid animal and causes inflammation of the brain in humans and other mammals. Transmission of

Methods

The materials for this review were published documents. The study reviewed the published literature on commonly used traditional medicinal plants for the treatment of rabies by using a web-based literature search strategy. Data for this review were generated from the published research findings on Ethiopian traditional medicinal plants on indifferent peer reviewed journals and proceedings using search words, Rabies in Ethiopia, medicinal plants, Ethno botanical studies and anti-rabies activity. Additional literature, including preelectronic literature such as dissertations, theses, and other materials were sourced.

Ethiopian Antirabies Plants

The Ethiopians employed a wide variety of traditional treatment in cases of bites by dogs believed to be rabitic. It was given free of charge to anyone in need, and was supposed to be one hundred percent successful. Most traditional Ethiopian medicines for rabies came from the vegetable kingdom [7]. Eighty plant species claiming to have anti-rabies activity were reported. The plants represent 43 families and 68 genera with the most prominent families being Euphorbiaceae (8 species), Cucurbitaceae (7 species), Solanaceae and Fabaceae (each with 4 species) and Asteraceae (3 species). *Phytolacca dodecandra*, *Justica schimperiana*, *Ricinus communis*, *Brucea antidysenterica*, *Croton macrostachyus*, *Cucumis ficifolius*, *Salix subserrata*, *Calpurnia aurea*, *Euphorbia abyssinica* and *Stephania abyssinica* were the most commonly utilized medicinal plants for the management of rabies in Ethiopia [8].

Efficacy and Safety

Traditional medicinal plants have been considered safe as a result of the long history of use in the treatment of diseases based on knowledge accumulated over several centuries [9]. The belief that herbal-based healthcare products are safe and devoid of side effects is untrue and misleading. Herbs have been found to be capable of producing a wide range of side reactions; like, causing serious injuries, life-threatening conditions, and even death. This is due to confusing nomenclature and inaccurate plant identification; lack of pharmaceutical-level quality control at all stages of production; variations in levels of active ingredients in different plant parts and plants harvested at different stages of development; the geography, weather, soil, and other conditions specific to individual plants [10]. Recent scientific research has shown that many plants used as food or in traditional medicine are potentially toxic, mutagenic and carcinogenic [11]. Generally, medicinal plants were suggested to exert two types of adverse effects. The first is inherent to the consumed plant and includes toxicities related to an over-dosage and interaction with conventional drugs. The second is related to extrinsic factors such as the quality of the product, which may interfere with the merit of herbal therapy [12]. Adverse fatal side effects and cases of rabies deaths after traditional treatment with medicinal plants were the most problems reported by some health centers, like Ethiopian Public Health Institute (EPHI) in Ethiopia. Out of 80 plant species reported for their antirabies activities in Ethiopia, only 5 were scientifically investigated in vivo and/or in vitro. These were *Phytolacca dodecandra*, *Justica schimperiana*, *Croton*

macrostachyus, *Salix subserrata* and *Silene macroselen* and the evidence for their efficacy and safety discussed below.

Phytolacca dodecandra; Family; *Phytolaccaceae*

Phytolacca dodecandra have different medicinal uses. Parts of the *Phytolacca dodecandra* (endod) plant have been used as a detergent and as traditional medicine for centuries in Ethiopia. The use of endod against abortion and skin itching is most common, followed by treatment of gonorrhoea, leeches, intestinal worms, anthrax, and rabies. It is used against snake bites and rabies in which, chopped roots are soaked for a short time and the filtered suspension is drunk [13]. The efficacy of this medicinal plant against rabies were evaluated with modern pharmaceutical practices by few researchers in Ethiopia. The antirabies activities of hydroethanolic extract of root and leaves of *Phytolacca dodecandra* were evaluated in mice in which the leaves of this plant showed some antirabies effect at higher dose level (1000 mg/kg). The mean survival time of mice treated with roots of *Phytolacca dodecandra* extract at 300, 600 and 1000 mg/kg were 9.9, 12.2 and 10.36 days, respectively whereas, the mean survival time of group of mice treated with its leave extract at 300, 600 and 1000 mg/kg were 10.81, 8.18 and 22.83 days, respectively [14]. Demeke, et al evaluated the antirabies activity of root extract of *Phytolacca dodecandra* plant in mice at 5000 mg/kg which improved the survival period of experimental mice compared to control group infected with rabies virus [15].

The acute oral toxicity test of the 80% methanol extract of *Phytolacca dodecandra* root indicated that it did not cause gross behavioral changes and mortality within 24 h and up to 14 days later. Therefore, the LD50 was estimated to be greater than 2000 mg/kg in mice (Meharie, et al., 2021). An acute toxicity study revealed that female rats that received the aqueous leaf extract of *P. dodecandra* at the dose of 2048 mg/kg displayed a reduced appetite, sleepiness and excessive urination and shivering [14].

Justica schimperiana; Family; *Acanthaceae*

The efficacy of *Justica schimperiana* against rabies were evaluated in mice, and the crude extract of the leaf extract of the plant showed anti-rabies activity at different dose level. It showed a percentage survival of 11.1% (1/9) and mean survival period of 12.56 days at 300 mg/kg. At 5000 mg/kg dose level the plant showed a 22.2% (2/8) and 15 days percentage survival and mean survival periods, respectively [15].

In the oral acute toxicity test, the 80% methanolic leaf extract of *Justica schimperiana* at the limit dose of 2000 mg/kg body weight, was found to be safe. There was no mortality or remarkable signs of toxicity noted in the 14-day observation of the mice and hence, the LD50 of the plant extract is greater than 2000 mg/kg [16].

Croton macrostachyus; Family; *Euphorbiaceae*

Croton macrostachyus showed a good result in keeping mice infected with rabies from death. The percentage survival of mice treated with the root bark of this plant at 2000 mg/kg was observed 30% (3/10) percentage survival with 17.1 days mean survival time (Demeke Z, et al., 2019).

Acute toxicity studies in animal model demonstrated the relative safety of the plants extract. The results of toxicity studies of the crude and the solvent fraction of leaf of *Croton macrostachyus* showed LD50 value of greater than 5000 mg/kg. Physical and behavioural observations of the experimental mice revealed no visible signs of overt toxicity like lacrimation, loss of appetite, tremors, hair erection, salivation, diarrhoea and the like [17]. The acute toxicity determination of root bark extract of *Croton macrostachyus* were observed in mice revealed no significant values in terms of survival time when compared to negative control group [15].

Salix subserrata; Family; Salicaceae

[7] Describe a rabies cure, the one apparently used at Menelik's palace, was made from the roots of the *Salix subserrata* or *S. Alba* which was drunk in water or some other liquid. A study conducted on mice to evaluate the anti-rabies activity of the crude extracts of *Salix subserrata* revealed that chloroform and aqueous extracts of the plant were found to increase the survival time of mice significantly [18]. The safety of *Salix subserrata* is not yet established in Ethiopia.

Silene macroselen; Family; Caryophyllaceae

[18] Conducted a study on the evaluation of the efficacy of the crude extracts of *Salix subserrata* and *Silene macroselen* for the treatment of rabies in Ethiopia. The result revealed that a 1 day and 2 days' treatment groups of the chloroform extract of *Silene macroselen* and the methanol 80 % extract of the same plant in its 1 day and 3 days' treatment showed significant difference on survival time from the positive control group ($P < 0.05$) [19]. Deressa A, et al also reported that no mortality or visible signs of delayed toxicity were observed with the plant extract given up to 80 mg/kg within 7 days in mice.

Conclusion

The use of medicinal plants for the management of rabies is frequent in Ethiopia. The present review summarizes the findings on efficacy and safety status of such medicinal plants. Very few attempts have been made on different plant extracts used for the management of rabies in Ethiopia. However, even those most commonly used medicinal plants have not been fully investigated for their safety and antirabies activities. The chemical compound/s responsible for its anti-rabies activity is still not known. To fully understand the pharmacological and toxicological properties of those medicinal plants, it is important to study phytochemistry of such plants. A link should have made between the traditional uses of a plant part, the active compounds isolated from it and pharmacological tests confirming or not confirming the activity of these active compounds or of the plant extracts containing active compounds.

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