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ORIGINAL RESEARCH

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Crude ethanolic extract and fractions of *Buchholzia coriacea* modifies salivary secretion and electrolyte compositions in rat

Olugbenga Adeola Odukanmi, Adeola Temitope Salami, Muideen Olayemi Isa, Samuel Babafemi Olaleye
Laboratory for Gastrointestinal Secretion and Inflammation Research, Department of Physiology, University of Ibadan, Ibadan, Nigeria.

ABSTRACT

Background: Extract of *Buchholzia coriacea* (*BC*) has been reported for its potent antimalarial effect. Unlike certain established antimalarial drugs reported for their roles in modifying saliva flow and components, *BC* effect on saliva is unknown. The effect of *BC* on saliva flow and its components was investigated.

Materials and Methods: Thirty male Wistar rats 150.7 ± 13.3 g were used for the study. They were grouped into six (n = 5) and treated with the various component of *BC* extract for 2 weeks. Group 1 (control) received distilled water, groups 2–6 received 200 mg/kg of the oily portion of the extract, 100, 200 mg/kg of the crude extract, 200 mg/kg absolute ethanol, and 200 mg/kg aqueous ethanol fractions of *BC*, respectively. Body weight, salivary flow rate, electrolyte compositions, and salivary glands morphological changes were determined using standard methods. The values were expressed as mean ± standard error of mean, compared, analyzed and considered significant at $p < 0.05$.

Results: The ethanol fraction of *BC* reduced significantly the salivary flow rate (0.03 ± 0.00 ml/minute) compared with control (0.05 ± 0.00 ml/minute). *BC* oil (44.24 ± 1.18 mmol/l) significantly reduce Na^+ concentration compared to control (52.02 ± 2.52 mmol/l), absolute ethanol fraction (54.00 ± 1.59 mmol/l), and aqueous ethanol fractions (54.66 ± 1.66 mmol/l), respectively. The 200 mg/kg aqueous ethanol fraction of *BC* significantly increase HCO_3^- and K^+ concentration compared to control. There was a slight distortion on salivary gland of the *BC* treated groups compared to control.

Conclusion: This study suggests that *BC* modulates salivary flow rate and electrolytes composition in rats.

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Buchholzia coriacea; salivary flow; electrolytes; histology; rats

Introduction

Saliva is one of the most important glandular secretions of the gastrointestinal system. Its role in health and diseases cannot be over emphasized due to its contribution to oral cavity homeostasis which mirrors the entire internal environment [1]. Its use as a diagnostic fluid meets the demands for an inexpensive, non-invasive, and accessible diagnostic tool [2]. Saliva has been used to detect caries risk [3], periodontitis [4], oral cancer [5], breast cancer [6], salivary gland diseases [7], and systemic disorders, such as hepatitis and Human Immunodeficiency Virus (HIV) [8]. For instance, swift point of-care for HIV tests utilizes saliva, gingival crevicular fluid, or oral mucosal fluid to rapidly provide test results to patients [9]. This reality has led to increase emphasis and attention to salivary studies with different intervention.

Quite a lot of benefits have been attributed to the seeds and leaves of *Buchholzia coriacea* (*BC*) folklorically which earned it the name "wonder kola" [10,11], while few of these acclaimed benefits have gained scientific assertions, such as its use in the treatment of malaria. Certain fractions of methanolic extract of *BC* stem back revealed a high concentration-dependent antibacterial and antifungal activity comparable to standard antibiotics, such as Ampicillin and Tioconazole [12]. The ethanolic extract of *BC* seed triggered larval deaths of the infective stage larvae of *Haemonchus contortus* and

Contact Olugbenga Adeola Odukanmi ✉ odukanmi@yahoo.com Department of Physiology, University of Ibadan, Ibadan, Nigeria.

Heligmosomoides polygrus at several concentrations *in vitro* [13]. Several studies have described the critical role of *BC*, Olaleye et al. [14] asserted the analgesic and anti-inflammatory properties of *BC* in rats, while Owonikoko et al. [15] and Salami et al. [16] both reported the gastroprotective properties of *BC* in acetic acetic acid induced gastric ulcer and ischemia-reperfusion ulcer models of rats, respectively.

The use of the extract of *BC* in the treatment of malaria infection and fever with a potent effect when mixed with palm oil and taken orally has been described [17]. There are also reports that certain antimalarial therapy, hydroxychloroquine can promote reduced functions of salivary glands [18]. The suggestion that *BC* might take an exception to these reported unwanted effect of conventional antimalarial warranted this current study. More so, the dearth of scientific report on the effect of *BC* in salivary constituent and its flow rate reinforced the aim of the current study.

Materials and Methods

Drugs and chemicals

Pilocarpine was obtained as a gift sample from Dr. Taye Lasisi, Department of Physiology, University of Ibadan, Ibadan, Nigeria. All other chemicals and reagents were purchased from authenticated suppliers and were of analytical grade.

Extraction of crude extract of Buchholzia coriacea

The dried seeds of *BC* were purchased locally from Oje Market in Ibadan. The plant was identified, deposited, and given a voucher number of FHI-110096 at the Forestry Research Institute of Nigeria, Ibadan, Nigeria. The seeds were rinsed with distilled water to remove adhering specks, after which they were sliced into lesser pieces and air dried at room temperature for four weeks before being milled into a powdery form [16]. Ethanol extract of the macerated seed was obtained using the Soxhlet apparatus as described by Harbone [19]. A portion of the extract obtained was filtered and the filtrate evaporated to dryness in a glass jar at normal atmospheric temperature and pressure. The crude extract was stored at 4°C until use and was administered orally to experimental animals at 100 and 200 mg/kg body weight, respectively.

Fractionation of Buchholzia coriacea crude extract

A portion of the crude extract was further dissolved in ethanol only or distilled water with ethanol in ratio 1:1 by the use of a separating glass funnel. Crude extract of *BC* that dissolved in ethanol and water are termed absolute ethanol fraction and aqueous ethanol fraction respectively. All the fractions obtained were collected in a different glass jar in a desiccator to allow evaporation to take place. Fractions of *BC* obtained after evaporation to dryness were stored at 4°C until use. *BC* Oil fraction was obtained by careful decantation of the oily and less viscous supernatant portion from the surface of the crude extract.

Animal and grouping

Thirty male rats of the Wistar strain (7-week old, 150.7 ± 13.3 g) were used. The animals were obtained from the Central Animal House, University of Ibadan, Nigeria. The rats were housed in well ventilated cages and acclimatized for 2 weeks prior to commencement of experimental procedures. They were fed freely with standard commercial rat pellets (Ladokun Feeds Limited, Nigeria) and allowed free access to drinking water prior to the start of the experiment. The rats were randomly divided into six groups (n = 5 per group). Group 1 was the control and received distilled water instead of *BC* extract. Groups 2–6 received 200 mg/kg of the oily portion of the extract, 100, 200 mg/kg of the crude extract, 200 mg/kg absolute ethanol, and 200 mg/kg aqueous ethanol fractions of *BC*, respectively, daily for 2 weeks. All experiments were conducted according to the guidelines and were approved by the University of Ibadan Animal Care and Use Research Ethics Committee (Assigned number—UI-ACUREC/17/0058), this conforms to the International Guidelines for Handling of Laboratory Animals [20].

Collection and analysis of saliva

The rats were fasted for 12 hours and were anesthetized with ketamine (75 mg/kg) prior to determination of salivary flow rate. They were restrained on the dissecting board that was inclined at an angle of 15° to the horizontal plane. The rats head were positioned sideways over the collecting bottles in a way that would prevent contamination by nasal secretion. Salivary secretion was stimulated with a su*bc*utaneous injection of 2.5 mg/kg b. wt. pilocarpine [21], saliva was allowed to drool and the flow was collected for 15 minutes from the start of the first drop of saliva. Rates of resting saliva secretions were expressed in ml/minute. Volumes of the secretions collected were measured and followed by storage at −20°C until use. Subsequently, the samples were defrosted at room temperature and

then centrifuged at 6,000 rpm for 10 minutes before use, to remove extrinsic contamination elements, such as oral epithelial cells, micro-organisms, and food debris among others as explained by Taylor and Preshaw [22]. For the determination of salivary ions, saliva was diluted in 1/100 and K^+, Na^+ concentration was determined using flame emission spectrophotometer, while concentrations of Cl^- and HCO_3^- were determined by titration method.

Statistical analysis

Values were expressed as mean ± standard error of mean of five animals per group. Comparisons were made by using one way Analysis of Variance followed by post hoc Newman–Keul's test with Graphpad prism, version 5.0. Values were considered significant at $p < 0.05$.

Results

Effect of Buchholzia coriacea treatment on body weight of animals

There was no significant change in the weight of animals treated with *BC* compared with the control before and after administration of both crude extract and fractions (Table 1).

Effect of Buchholzia coriacea on salivary flow rate

Treatment with 200 mg/kg aqueous-ethanol fraction of *BC* reduced salivary flow rate significantly (0.03 ± 0.00 ml/minute) compared with animals in the control group (0.05 ± 0.00 ml/minute) and those treated with *BC* oil. Aqueous fraction also reduced flow rate significantly compared to animals treated with absolute ethanol fraction and (200 mg) of the crude extract, (Fig. 1).

Effect of Buchholzia coriacea treatment on salivary electrolytes

Treatment with 200 mg/kg *BC* oil reduced sodium ion concentrations significantly (44.24 ± 1.18 ppm) compared to the control (52.02 ± 2.52 ppm), 100*BC* (51.04 ± 1.52 ppm), 200*BC* (47.72 ± 1.19 ppm), ethanolic fraction (54.00 ± 1.34 ppm) and aqueous fraction (54.66 ± 1.29 ppm) (Figure 2). Treatment with fractions of *BC* significantly increased potassium ion concentration compared to the control group (Fig. 2). Figure 2 further shows a significant

Table 1. Percentage change in body weight after *Buchholzia coriacea* administration.

% Weight Difference	Ctr	B. Oil	Crude B100	Crude B200	Et.F	Aq-EF
Before treatment (%)	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
After treatment (%)	113.3 ± 6.2	109.1 ± 6.1^{ns}	111.7 ± 5.5^{ns}	112.8 ± 4.2^{ns}	118.0 ± 2.3^{ns}	117.2 ± 2.8^{ns}
% Change in body weight	13.3 ± 0.4	09.1 ± 2.9^{ns}	11.7 ± 1.2^{ns}	12.8 ± 2.7^{ns}	18.0 ± 2.2^{ns}	17.2 ± 2.1^{ns}

n = 5, Ctr = control, B.Oil = *Buchholzia coriacea* oil, Crude B100 = 100mg *Buchholzia coriacea,* Crude B200 = 200mg *Buchholzia coriacea,* Et.F = Absolute ethanol fraction of *Buchholzia coriacea,* Aq-EF = Aqueous ethanol fraction of *Buchholzia coriacea.*

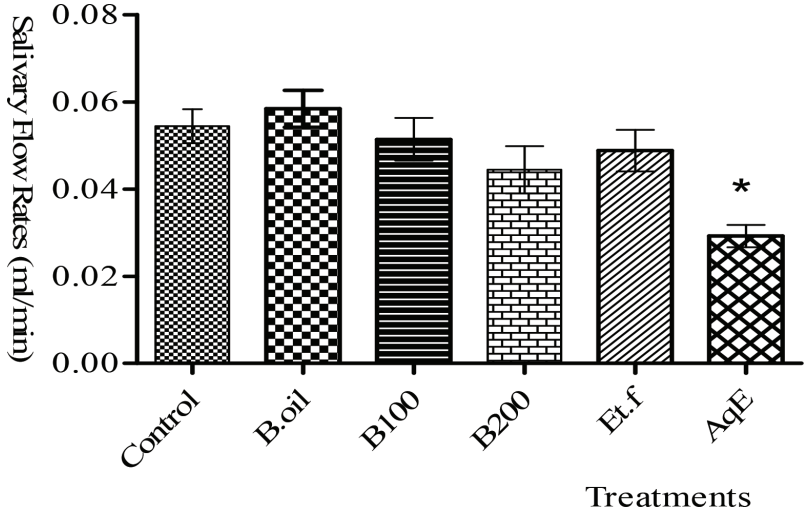

Figure 1. Effect of *Buchholzia coriacea* on salivary flow rate of rats.
*significantly decreased compared to control.

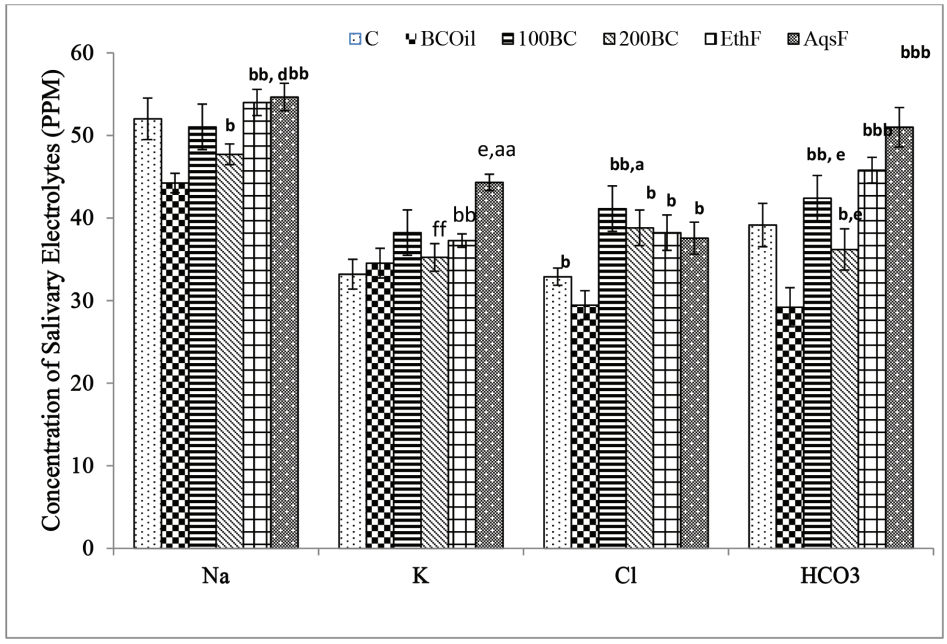

Figure 2. Effect of crude extract and fractions of *Buchholzia coriacea* on salivary electrolyte composition. [a]significant increase at $p < 0.05$ compared with control, [aa]significant increase at $p < 0.01$ compared with control, [b]significant increase at $p < 0.05$ compared with *B. coriacea* oil, [bb]significant increase at $p < 0.01$ compared with *B. coriacea* oil, [bbb]significant increase at $p < 0.001$ compared with *B. coriacea* oil, [e]significant increase at $p < 0.05$ compared with ethanol fraction, [f]indicate significant at $p < 0.05$ compared with aqueous-ethanol fraction.

decrease in the chloride ion concentration of the *BC* oil (29.45 ± 1.09 ppm) compared with the control (32.9 ± 1.23 ppm), 100*BC* (41.14 ± 2.78 ppm), 200*BC* (38.82 ± 2.19 ppm), EthF (38.230 ± 2.04 ppm) and AqsF (37.56 ± 1.69 ppm). Thus, apart from *BC* oil, all other extracts and fractions significantly increased salivary chloride ion compared to the control, (Fig. 2). Treatment with 200 mg/kg aqueous fraction of *BC* (51.00 ± 2.39) increased bicarbonate ion significantly, while *BC* oil reduced bicarbonate ion significantly (29.20 ± 2.37) compared with the control (39.16 ± 2.62) (Fig. 2).

Effect of Buchholzia coriacea on the micro architecture of salivary glands

Figure 3 shows the effect of *BC* on salivary glands following treatments with the extracts. *BC* oil indicated slight distortion in the architecture of the fibrous tissue evidenced by dilated secretory ducts while serous acini appear normal compared with control. The *BC* 100 mg moderately increased connective tissue compared to control. *BC* 200 mg, revealed distortion of the salivary gland architecture demonstrated by fibrotic changes, reduced vascularization, and mildly thickened secretory duct compared to the control group. Eth-f retained normal salivary gland architecture. The AqEf group also retained normal architecture of lobules with dividing normal septa, normal secretory duct and the serous acini compared to control.

Discussion

Salivary secretion is important to the maintenance of body homeostasis and certain antimalarial therapy can promote hypofunction of salivary glands [18]. *BC* was reported to possess antimalarial properties in mice [17,23]. This current study was to determine the relationship between the previously reported drooling effect of some established antimalarial therapy and *BC*.

The various treatment doses with the extracts and fractions of *BC* showed no change in weight of animals which is in line with earlier reports that *BC* extracts sustain animal body weight and weights of visceral organs like lung, liver, heart, and kidney compared to control [24]. However, Salami et al. [16] reported a decrease in percentage weight change during 7 weeks of supplemented feeds with varying quantities of *BC* seeds in rats. The possible reason for this speckled report on *BC* could be due to the different duration and the diverse components and

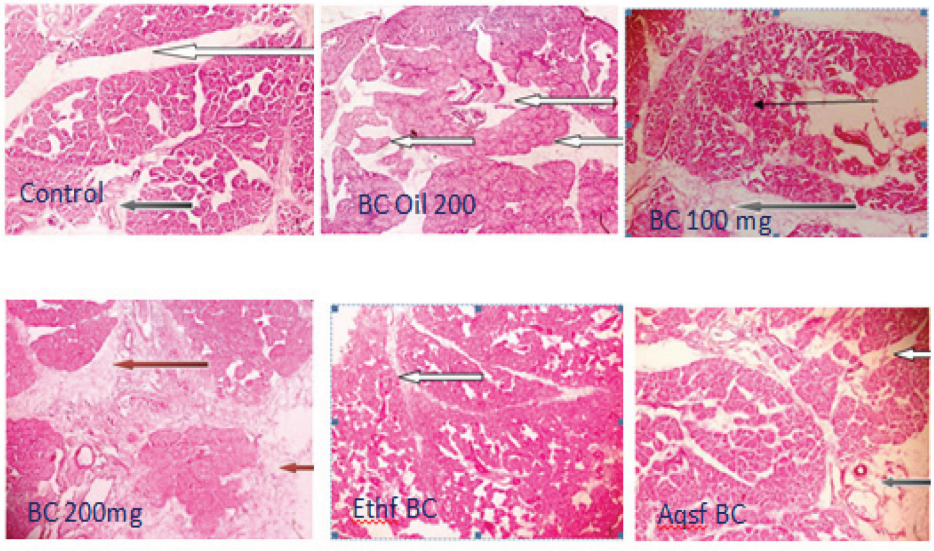

Figure 3. Representative photomicrograph of parotid gland following treatment with *B.Coriacea*. (Haematoxylin and Eosin stain, Magnification ×100). Control—normal architecture with normal septa (white arrow), normal duct (black arrow) and serous acini (slender arrow). *BC* Oil—poor architecture seen in fibrous area (red arrow) with dilated secretory ducts (black arrow), serous acini (slender arrow) appears normal. *BC* 100 mg—moderately increased connective tissue (black and slender arrows). *BC* 200 mg—poor architecture with fibrotic layer (red arrow), reduced vascularization and mildly thickened secretory duct (black arrow). Eth-f—normal architecture with normal lobules and septa (white arrow), normal serous acini (slender arrow), with presence of mild vascular congestion (black arrow). AqEf—Normal architecture of lobules with dividing normal septa (white arrow), normal secretory duct (black arrow) and the serous acini (slender arrow).

quantity of substances of *BC* that the animals were exposed to. The initial report was with pure *BC* seeds supplemented with feeds for 7 weeks, whereas the index result was from extracts and fractions of *BC* given to animals for 2 weeks. It is apparent that a longer period of exposure and a possible increase in the dosage of extracts and fractions of *BC* could as well make an impact on the body weight.

Malaria is one of the systemic diseases associated with changes in salivary flow and compositions [25]. In the report of Lasisi et al. [25] on salivary flow rate in malaria patients, they found a reduced flow rate and related it to the possible dehydration following the usual increase in body temperature of malaria patients. The study did not state whether the patients were on any antimalarial medication or not. It is however established that majority of antimalarial are excreted in the urine and saliva [26].

The reduced salivary flow rate in the aqueous-ethanol fraction of *BC* compared with control is in agreement with the earlier reports on certain antimalarial drugs, such as amodiaquine and chloroquine which described excessive salivation following treatment [27,28]. None of the other extract of *BC* was observed to have produced excessive or reduced salivation in comparison to the control. It is well established that a reduction in flow rate of saliva could be extremely damaging. It predisposes to dental caries; erosion of the teeth, oral candidiasis and so on [29], reduced saliva secretion promotes xerostomia and inhibits a number of physiologic processes associated with saliva functions [30,31].

Salivary electrolyte changes report in malaria positive and those who were negative for malaria parasites in a case-control study reported by Lasisi et al. [25] hardly spot any significant variation. It was also not stated if the patients used for the study were on any antimalarial medication as at the time of carrying out the study [25]. The reduced concentration of sodium, chloride and bicarbonate ions of the *BC* oil treated groups in this study indicates active reabsorptive process of the ductal acini in the groups treated with the oil component of the extract. Similar reduction on serum sodium level of experimental animals were reported on the effect of root extract of *Sarcocephalus latifolius,* which also has strong antimalarial potency [32],

while on the contrary, treatment with both P-alaxin and Coartem increased serum Na+ concentration as reported by [33].

The increased chloride ion and bicarbonate of the ethanolic and aqueous extracts were proofs of efficient secretory functions of the ductal acini following treatment with the fractions. Bicarbonate ion is of relevance in maintenance of acid-base balance of the body, the observed decrease in bicarbonate ion could be an indication of low pH of the body and possibly indicating systemic or oral acidosis.

It is not unlikely for herbal substances to either cause hypokalaemia or hyperkalaemia [34]. So, there is an evidence of the aqueous fraction of *BC* causing increase salivary potassium levels, it should be a consideration while attempting to exploit its numerous medicinal potentials.

The poor histoarchitecture observed in parotid gland of the groups treated with 200 mg/kg crude extract and oil might be an indication of a possible toxic effect on the gland. However, this study did not investigate the effect of withdrawal of the extract on the gland to assess possible reversal of the aberrant salivary structure. To the best of our knowledge, there are no previous reports on histoarchitecture of salivary glands following treatment with *BC*.

In conclusion, this study ascertain reduction in salivary secretion from oral use of *BC* and this property further strengthens its importance in the treatment of plasmodium if eventually cleared for that purpose in the future. However, the possible mechanism of action of the extract of *BC* in reducing salivary secretion and the modification of its electrolyte compositions was not elucidated in this study.

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Conflict of interest

The authors declared that they have no conflict of interest.

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