



Biochemical Effect of *Psidium guajava* on Experimentally induced diarrhea in mice

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ABSTRACT

In the present study, the potential therapeutic effect of aqueous extract of *psidium guajava* leaves (GLE) on serum (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Creatinine, Uric acid ,Lipase , Lactase , Na^+/K^+ ATPase and NF- KB) in mice suffering from diarrhea induced by bovine viral diarrhea virus (BVDV) infection was evaluated. Fourty –five male albino mice were divided into 3 equal groups (15 each). Group1 (normal control group), mice not infected with the virus and served as a control group. Group2 (diarrhea –induced group) ,mice infected with BVDV at a dose of 0.25 ml once orally. Group 3 (*P.guajava* –treated group) ,Mice infected with BVDV at a dose of 0.25 ml once orally and treated orally with 0.5 ml aqueous extract of *P. guajava* leaves at a dose of (400 mg/kg b.wt /day) for 2 weeks . blood samples were collected from all groups after 2 weeks of treatment. The obtained results showed that, mice infected with BVDV had a significant increase in serum level of (glucose, creatinine, uric acid , NF-KB , ALT and AST) Meanwhile, (Lipase, Lactase and Na^+/K^+ ATPase)activities were significantly decreased when compared to normal control group. Administration of diarrhea-induced group with aqueous extract of *P. guajava* (GLE) significantly restored all biochemical parameters nearly to normal where serum levels of (glucose, creatinine, uric acid , NF-KB , ALT and AST) were significantly decreased Meanwhile, serum (Lipase, Lactase and Na^+/K^+ ATPase) activities were significantly increased when compared to diarrhea -induced group .

Keywords: BVDV, diarrhea, GLE, , Na^+/K^+ ATPase, NF- KB.

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1. INTRODUCTION

Diarrhea is defined as the passage of three or more watery or looser-than-usual stools within the preceding 24 hours for less than 2 weeks' duration (Nakagomi and Cunliffe, 2013).

Bovine viral diarrhea virus infection can cause severe economic losses due to decreased fertility and milk production, slow fetal growth, diarrhea, respiratory symptoms, reproductive dysfunctions

such as abortion, teratogenesis, embryonic resorption, fetal mummification and stillbirth, immunological dysfunctions, concurrent infections, impaired herd performance, and the dreaded state of persistent infection (PI) in calves (Brock, 2004) . Bovine viral diarrhea virus has been found in sheep, goats, pigs, buffaloes and wildlife, although the chance of transmission to or from

cattle has not been fully established. Transmission between sheep and cattle has been experimentally proven (Lamm et al., 2009). Isolation of the virus in wild ruminant animals such as deer and elk in North America has been reported (Grooms and Keilen, 2002). Mice can be infected with bovine viral diarrhea virus (Seong et al., 2015).

Today, there is increasing interest in discovering new bioactive compounds derived from ethnomedicine. The pharmacological research in vitro as well as in vivo has been widely used to demonstrate the potential of the extracts from the leaves for the co-treatment of different ailments with high prevalence worldwide, upholding the traditional medicine in cases such as diabetes mellitus, cardiovascular diseases, cancer, and parasitic infections (Cerio et al., 2017).

Psidium guajava L., popularly known as guava, is a small tree belonging to the myrtle family (Myrtaceae) (Morton, 1987). Native to tropical areas from southern Mexico northern South America, guava trees have been grown by many other countries having tropical and subtropical climates, thus allowing production around the world (Salazar et al., 2006). *P. guajava* is mainly known for its antispasmodic and antimicrobial properties in the treatment of diarrhoea and dysentery. Many pharmacological studies have demonstrated the ability of this plant to exhibit antioxidant, hepatoprotection, anti-allergy, antigenotoxic, cytotoxic, cardioactive, anticough, anti-inflammatory and antinociceptive activities, supporting its traditional uses (Gutiérrez et al., 2008).

Guava is known to be rich in phytochemical compounds such as flavonoids, phenols, terpenes, and essential oils. Much of guava's therapeutic activity is attributed to these compounds (Holetz, 2002).

Aim of the work

This study aimed to evaluate treatment of diarrhea with aqueous extract of *psidium guajava* leaves on serum (glucose, creatinine, uric acid, NF-KB, ALT, AST, Lipase, Lactase and Na⁺/K⁺ ATPase).

2. MATERIAL AND METHODS

2.1. Experimental animals:

45 male mice (each 6-8 week old of weighting 25-30 g) were purchased from laboratory animals research center, Faculty Of Veterinary Medicine, Benha University.

Mice were housed in separate metal cages, fresh and clean drinking water was supplied ad libitum. Mice were kept at constant environmental and nutritional conditions. Mice were left for 15 day before experiment for adaptation.

2.2. Chemicals and Natural Compounds

2.2.1. Aqueous Extract of *psidium guajava* leaves

p. guajava leaves were collected from a local garden in El-Gharbiya Governorate. Leaves were washed with water, air dried and finely powdered in a mechanical grinder. Samples of the powdered guava leaves were extracted separately by boiling for 10 min (Metwally et al., 2011).

2.2.2. Dosage

The extract was used at a dose of (400 mg/kg b.wt /day) orally for 2 weeks (Ojewole et al., 2008).

2.3. Experimental Design:

45 Mice were randomly divided into 3 main equal groups (15 mice each) and placed in individual cages as follow:

Group1 (normal control group), mice not infected with the virus. Group2 (Diarrhea-induced group), mice infected with BVDV at a dose of 0.25 ml once, orally

Group3 (*p. guajava* -treated group) mice infected with BVDV at dose of 0.25 ml once, orally and treated orally with 0.5 ml aqueous extract of *guajava*

leaves (GLE) at adose of (400 mg/kg b.wt /day) for 2 weeks .

2.4.Sampling:

Blood samples were collected once from all aniaml groups after 2 weeks from the onset of Treatment with p.guajava extract .Serum was separated by centrifugation of blood samples at 3000 r. p. m for 15 min. The clean, clear serum was separated by pasture pipette and received in dry sterile samples tubes, processed directly for glucose determination , then kept in a deep freeze at - 20 until used for subsequent biochemical analysis that

done to evaluate Biochemical Effect of Psidium guajava on Experimentally induced diarrhea in mice for the following biochemical parameters:

glucose (Trinder , 1969), (ALT,AST (Schumann et al., 2002)) , Creatinine (Tietz, 1995), Uric acid (Schultz et al., 1984) , Lipase (Elabscience® (7th Edition, revised in April, 2017, catalog No:E-EL-R244196T), Lactase (cloud – clone corp(11th Edition ,Revised in July, 2013),Na⁺/K⁺ATP(My Biosource .com catalog number: MBS7245054) and NF B (My BioSource .com catalog number 722386).

Table (1) effect of Psidium guajava on (glucose, creatinine, uric acid (mg/dl)) , (ALT , AST(U/l)) , (Lipase, NF-KB,(pg/ml)),(Lactase and Na⁺/K⁺ ATPase (ng/ml)) in experimentally induced diarrhea in mice

Parameters groups	Glucose (mg/dl)	ALT (U/l)	AST (U/l)	Creatinine (mg/dl)	UA (mg/dl)	Lipase (pg/ml)	Na ⁺ /K ⁺ ATPase (ng/ml)	NF-KB (pg/ml)
Control group	92.00 ± 1.52 ^c	36.34 ± 0.88 ^c	41.33 ± 0.88 ^c	0.73 ± 0.01 ^c	3.30 ± 0.08 ^c	120.40 ± 5.18 ^a	12.71 ± 0.11 ^a	45.73 ± 1.63 ^c
Diarrhea-induced group	317.33 ± 2.18 ^a	107.67 ± 2.41 ^a	91.05 ± 1.73 ^a	1.46 ± 0.03 ^a	6.47 ± 0.15 ^a	35.43 ± 1.84 ^c	1.80 ± 0.12 ^c	100.66 ± 5.23 ^a
GLE-treated group	145.00 ± 2.64 ^b	84.72 ± 1.45 ^b	66.67 ± 1.45 ^b	1.06 ± 0.03 ^b	5.24 ± 0.08 ^b	83.16 ± 3.44 ^b	3.22 ± 0.15 ^b	80.67 ± 1.76 ^b

(Mean ± S.E), S.E = Standard error. a significant <0.05.

Means Values with different Superscript letters in the same column and in the same row are significantly different at (p< 0.05).

2.6. Statistical analysis:

The obtained data were statistically analyzed by one-way analysis of variance (ANOVA) followed by the Duncan, s multiple test. All analyses were performed usin the statistical package for social science (SPSS, 13.0 software). Values at 0.05 were considered to be significant(Steel et al.,1997).

3.RESULTS :

Table (1) effect of psidium guajava on (glucose, creatinine, uric acid (mg/dl)) , (ALT , AST(U/l)) , (Lipase,NF-KB,(pg/ml)),(Lactase and Na⁺/K⁺ ATPase (ng/ml)) in experimentally induced diarrhea in mice .

4. DISSCUSSION

Acute diarrhea, defined as an increase frequency of defecation (three or more times per day or at least 200 grams of stool per day) lasting less than 14 days,

The obtained results in table (1) revealed that , diarrhea –induced group had a significant increase in serum (glucose, ALT, AST, Creatinine, Uric acid and NF -KB) Meanwhile,a significant decrease in serum activity of (Lipase, Lactase and Na⁺/K⁺ ATPase) when compared to normal control group .Treatment of mice suffering from diarrhea with aqueous extract of guajava leaves (GLE) resulted in significant decrease in serum(glucose, Creatinine, Uric acid , NF -KB , AST and ALT) Meanwhile a significant increase in serum activity of (Lipase, Lactase and Na⁺/K⁺ ATPase) enzymes when compared with diarrhea-induced group.

may be accompanied by nausea, vomiting, abdominal cramping, clinically significant symptoms, or malnutrition (Thielman and Guerrant,2004). Acute diarrhea is

among the most common problems encountered by the physician in the developing countries. Viruses are the major cause of diarrhea worldwide (Kc et al., 2006). Increased serum glucose level in diarrhea-group was agreed with (Matsuda and Taniyamay, 2013) who found that increased blood glucose level caused by persistent BDV infection is due to the gradual and selective destruction of B-cells of pancreatic islets. Treatment of infected group with extracts of GLE resulted in decreased serum glucose level.

In GLE-treated group this may be result from the activities of hepatic hexokinase and glucose-6-phosphate dehydrogenase observed in diabetic rats fed with aqueous as well as ethanolic extracts and increased phosphofructokinase activity only in aqueous extract (Shen et al., 2008).

Increased serum (ALT and AST) enzymes in bvdv-infected group was agree with (Teitelbaum and Daghistani, 2007) who found that, rotavirus commonly causes elevation of liver transaminases. Also Epstein Barr virus (EBV) is a member of the herpes virus family, infection causes a symptomatic liver-associated enzyme abnormalities in 80 to 90% of cases which are often unrecognized. Acute EBV infections is associated with moderate elevations in the transaminase activities. Serum (ALT and AST) values was decreased in GLE-treated group, These results was in agreement (Qian and Nihorimber, 2004) who recorded that, *psidium guajava* leaf extract is a known antioxidant and different extracts of this plant including the water extract are reported to increase the reduction of 2,2-diphenyl-1-picrylhydrazyl (PPH)

Increased serum creatinine level in diarrhea-group was agreed with (Kc et al., 2006) who found that, in patients presenting with acute gastroenteritis

there is a significant number of them showed increased level of serum urea and creatinine. In GLE-treated group there is a significant decrease in serum creatinine level compared to diarrhea-group. These results are in harmony with (Olufunke et al., 2016) who stated that, the use of the guava leaf extract alone showed nephroprotective properties that the creatinine level was significantly lower in Group C (extract only), Effects which, may be due to the antioxidant and free radical scavenging properties of some of the components of the extract. Increased serum uric acid level in diarrhea-group was agreed with (Adler et al., 1982) who reported that, elevated uric acid level was found in 80% of dehydrated patients admitted with diarrhea. (Matsuo et al., 2016) indicates the physiological and pathophysiological importance of intestinal epithelium as an excretion pathway besides an absorption pathway. Furthermore, increased serum uric acid could be a useful marker not only for dehydration but also epithelial impairment of intestine. UA was significantly decreased in GLE-treated group. These results are in agreement with the results of (Ironi et al., 2016) who demonstrated that, flavonoids and phenolic acids in the leaves could contribute to the prevention and amelioration of gout and hypertension, since, in rat-tissues homogenates, they inhibit the activity of two enzymes related to the development of both diseases. Diarrhea-group showed significant decrease in lipase activity. Treatment of diarrhea-group with GLE resulted in significant increase in lipase activity, and this may be due to flavonoids and other phenolic compounds act as porcine pancreatic lipase enzyme inhibitors by binding to the enzyme-substrate complex and reducing the lipid absorption (Villa-Ruano et al., 2013).

Diarrhea-group showed significant decrease in lactase activity. Treatment of infected group with GLE resulted in significant increase in lipase enzyme activity, and these results are in harmony with (Önning and Asp 1995) who found that, Oat saponins (a mixture of avenacosides A and B) *in vivo* not show inhibition in lactase activity in rats, probably due to far lower concentrations of saponins in their diets (low avenacoside concentrations found in oats).

Decreased serum Na^+/K^+ -ATPase enzyme in Diarrhea-group was in harmony with (Hackstadt and Mallavia, 1982) who suggested that observed depression of active K^+ uptake may represent a secondary effect of virus modification of the cytoplasmic membrane resulting in changes in membrane fluidity which in turn decrease the activity of the Na^+/K^+ -ATPase. The mechanism by which the activity of the Na^+/K^+ -ATPase is reduced is not clear. Also (Saha et al., 2014) support these results by using a rabbit model of chronic intestinal inflammation, which resembles human IBD, he found that Na^+/K^+ -ATPase in villus cells decreased. In GLE-treated group, there was a significant increase in Na^+/K^+ -ATPase activity. These results are in agreement with (Yu et al., 2016) who reported that, Quercetin-stimulated chloride secretion was partly decreased by the Na^+/K^+ -ATPase inhibitor ouabain. This suggested the important role of Na^+/K^+ -ATPase and K^+ channels in quercetin-induced Cl^- secretion.

Increased serum NF- κ B concentration in Diarrheal-group was agreed with (Santoro et al., 2003) who supports these results and stated that, Activation of NF- κ B is hallmark of most viral infections, and most viruses require it as transcriptional activator to express viral genes. Treatment of infected group with GLE

decreased serum NF- κ B concentration. These results are in agreement with (Camuesco et al., 2004) who proposed that, biochemical anti-inflammatory effects of quercitrin might be related to a decrease in inducible nitric oxide synthase (iNOS) expression through down-regulation of NF- κ B in colonic tissue.

Recommendation

Administration of guajava aqueous extract is very important against diarrhea resulted from infection with virus and may be useful against diarrhea resulted from any other reason.

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