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Protective role of Gum Arabic(*Acacia Senegal)* on oxidative stress in diabetic and adenine–induced chronic renal failure in rats

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Abstract : Oxidative stress is a global health concern associated with severe morbidity and mortality; which in turn affects diabetes and kidney failure disease. Administration ofgum arabic (GA) as a natural product acts a key role in the therapeutic strategy. Results indicate that GA contain high levels of phenolic compounds (which are considered antioxidant compounds), high antioxidant activity. Fractionation of sugars in GA resulted in constitution of D-galactose as a predominant sugar followed by L-arabinose. HPLC fractionation of phenolic compounds in GA reveals a high content of catechin and epicatechin. The administration of GA at 15% was the best treatment in diabetic and chronic kidney disease rats that enhanced the activities of Glutathione peroxidase (GPx) recording 17.820 and 15.952 (IU/mg protein), respectively; Superoxide dismutase (SOD) recording 3.600 and 3.500(IU/mg protein), respectively and catalase (Cat) recording 50.260 and 42.102 (IU/mg protein), respectively in comparison to other treatments and positive control.

Introduction

Gum arabic (*Acacia Senegal L. willd)* is edible, dried, gummy exudates from the stems and branches that is rich in non-viscous soluble fiber [1-3]. These trees are abundant in the central Sudan, Central and West Africa.

Gum arabic has many uses in industries including soft drinks, textile, pottery, cosmetics and pharmaceutical industries as stabilizer, thickening agent andemulsifier[3-4].

Gum arabic, a natural composite polysaccharide derived from exudates of *A. senegal* trees. The major fraction is a highly branched polysaccharide consisting of galactose backbone with linked branches of arabinose and rhamnose, which terminate in glucuronic acid found in nature as magnesium, potassium and calcium salt[5].

Gum arabic is primarily indigestible to both humans and animals. It is not degraded in the small intestine, but fermented in the large intestine by microorganisms to short-chain organic acids, particularly propionic acid.

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Despite the fact that GA is widely used as a vehicle for drugs in experimental physiological and pharmacological experiments and is assumed to be an "inert" substance, some recent reports have claimed that GA possesses antioxidant and nephroprotectant effects [2].

Gum arabic is rich in dietary fiber that is derived from dried exudates of *A. senegal* [6], It contains a high molecular weight (lipoprotein) heterogeneous gum polysaccharides [7].

In recent years, oxidative stress has been involved in the progression of male infertility [8]. The experimental evidence has been implicated that these damaging processes are caused by free radicals [9]. The deleterious effects of oxidative stress come from either an increased amount of reactive oxygen species(ROS) production [10-11]or a decrease of natural cell antioxidant capacity of an organism [12]. However, the utilization of foods rich with antioxidant phytochemicals may reducethe deleterious effects caused by oxidative stress [13]. Oxidative stress (OS) is a condition characterized by inconsistency between pro-oxidant molecules including reactive oxygen species (ROS) and nitrogen species, and antioxidant defenses [14-15].

Diabetes mellitus is a general term for heterogeneous disturbances of metabolism for which the main finding is chronic hyperglycaemia. The cause is either impaired insulin secretion or impaired insulin action or both. Type 1 Diabetes ▸ β-cell destruction which leads to absolute insulin deficiency. Type 2 Diabetes ▸ Can range from predominant insulin resistance with relative insulin deficiency to prevailing defective secretion with insulin resistance. ▸ Is frequently associated with other problems of the so-called metabolic syndrome[16]**.**

Chronic kidney disease (CKD), a worldwide health problem, is a slowly progressive disorder that might lead to end-stage renal disease (ESRD). The prevalence of CKD has grown rapidly in both the developed and developing countriesis now considered a key determinant of the poor health outcomes[17-18]. CKD is characterized by progressive deterioration of kidney function, which develops eventually into a terminal stage of chronic kidney failure (CKF).

Several factors influence the onset and progression of this CKD, such asobesity, hypertension and *Diabetes mellitus*. Beyond these factors,there is evidence of a pathophysiological role for inflammation andoxidative stress in CKD and its complications [19]. These two events are prominent features of CKD and its complications in humans [20-24]. Increased oxygen radical formation was foundin CKD, in the presence of a reduced antioxidant defense [25].Furthermore, markers of oxidative stress and inflammation are increased, like lipid peroxidation and glutathione content, or C-reactive protein (CRP) and IL-6 [26-28]. Oxidative stress and inflammation are also major mediators of the disease, exerting similar effects in the surgically-induced chronic renal failure (CRF)in rats [29-30].

[31]revealed that GA decreased the weight gain and inhibited intestinal glucose absorption by down-regulation of the membrane abundance. Moreover, GA treatment significantly reduced urinary glucose excretion, Na+ excretion and urinary volume [32].

Gum arabic (GA) has been used in the treatment of chronic renal failure. Renal effects of GA including decrease of plasma phosphate concentration, lowering of blood pressure and reduction of proteinuria. Moreover, GA exerts several extra-renal effects with therapeutic potential, such as slowing of intestinal glucose transport, which may be useful in the treatment of obesity and diabetes[33].

This research work aimed to study the active ingredients of gum Arabic, and investigate the antioxidant enzymes affecting oxidative stress caused by diabetes and chronic renal failure.

Materials and Methods

Materials:

Gum Arabic : The dried exudates (gum) from *Acacia senegal*were purchased from Aswan (Upper Egypt)**.** Streptozotocin (STZ)and Adenin were pure chemical fine obtained from Al Gomhorria company, Cairo.

Preparation and extraction of GA water extract:

Gum arabic where it is maximum active ingredients, 200 g. of gum Arabic powder were infused in 1 L of hot water for an hour in order to study its anti-inflammatory effects in diabetic and in Adenine-Induced chronic renal failure (AICRF) in rats.

Chemical composition of gum Arabic :

DPPH Assay

The antioxidant activity was evaluated by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method according to the procedure of [34]**.** The antioxidant activity was expressed as the percentage of decline of the absorbance, relative to the control, corresponding to the percentage of DPPH that was scavenged. The percentage of DPPH, which was scavenged (% DPPHsc), was calculated using %DPPHsc: %DPPHsc = $(A_{cont.}-A_{sam.}) \times 100/A_{cont.}$

Total phenols (g./100g. D.Wt.)

Total phenolics were analyzed spectrophotometrically using the method described by [35]. Results were expressed as g. gallic acid /100 g.D.Wt..

Total flavonoids (g./100g. D.Wt.)

Total flavonoids content was measured according to [36] per 100 g. dry weight.

Fractionation of sugars in gum Arabic :

Acid hydrolysis of sample was performed according to the method of[37]**.**

High Performance Liquid Chromatography (HPLC)

Fractionation of sugars content of the whole gum were determined by high performance liquid chromatography (HPLC) according to [38].

Fractionation of phenolic compounds in gum Arabic :

GA was extracted according to [39].

Fractionation of phenolic compounds in gum Arabic was performed by HPLC according to the method described by [40]**.**

Biological Experiment:

Experimental design:

The experimental rats were conducted according to committee for purpose of control and supervision of experiments on animals, 54 Adult males albino rats, weighing 180–200 g. fed with a standard basal diet, kept for 7 days as adaptation period before starting the experiment. Rats were then divided into 9 groups each containing 6 rats as follows**:**

Group 1 were given the standard diet (negative control) (-)
Group 2 Positive control (+)[Diabetic rats (treated by injection of STZ at a dose of 40 mg/kg body/ weight)].
Group 3 diabetic rats received 5% Gum Arabic,
Group 4 diabetic rats received 10 % Gum Arabic,
Group 5diabetic rats received 15 % Gum Arabic,
Group 6 [Chronic renal failure rats (CRF)(fed on basal diet plus 2 % adenine to induce chronic kidney disease (CKD) according to [41-42].
Group 7 CRF rats received 5% Gum Arabic,
Group 8 CRF rats received 10% Gum Arabic,
Group 9 CRF rats received 15% Gum Arabic.

The aforementioned intake doses of gum Arabic were administered three times a week.

Biochemical analysis of serum:

At the end of the experimental period (6 weeks), blood serum samples were collected.

Glucose in blood

Glucose was determined in the serum according to the colorimetric method by [43].

Determination of kidney function:

Serum urea was determined according to the method described by [44]**.** Uric acid in serum was determined according to the method of [45]**.** Creatinine in serum was determined according to the method of [46]**.**

Antioxidant enzyme activity

The activities of antioxidant enzymes including the glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase enzyme (CAT) were assayed using commercial assay kits according to the manufacturer's instructions.

The activities of GPx and CAT were measured by the methods described by [47-48], respectively. The activity of SOD was measured according to the method of [49]. All assays were measured with the clinical chemistry assay kits according to the manufacturer's recommended procedure (IU/mg protein).

Statistical analysis

Statistical analysis was carried out according to [50] using analysis of variance and the significance was determined using L.S.D. values at P=0.05 [51]**.**

Results and discussion

Chemical composition of GA :

Table (1) illustrates the active ingredients composition; namely antioxidant activity, total phenols and total flavonoids in gum Arabic. Results recorded antioxidant activity (66.707%) and total phenols (1.526 g./100g.), while it contains trace (nearly negligible) amounts of total flavonoids (0.0014 g./100g.).

Table (1) : Active ingredients composition of Gum Arabic

Antioxidant Activity%	**Total phenols g./100g.**	**Total flavonoids g./100g.**
66.707	1.526	0.0014

The aforementioned results were in agreement with those of [52] who mentioned that the aqueous extract of *A. catechu*has been shown to have antioxidant properties while possessed smaller amounts of flavonoids. Many studies have demonstrated *in vitro* antioxidant and free radical-scavenging activities of aqueous extracts of *A. catechu*[53-54].Also,[55]demonstrated thataqueous extracts of *A. catechu*of various plant parts were capable of inhibited lipid peroxidation in a rat liver microsomal preparation.

Furthermore, [52]also mentioned that the anti-inflammatory, antineoplastic, and analgesic activities are all believed to be due to the antioxidant activities.

Table (2) demonstrate the fractionation of sugars in gum arabic by HPLC. Results conclude that gum arabic contains D-galactose as a predominant sugar recording 41.37%, followed by L-arabinose (37.54%). Then came L-rhamnose and D-glucouronic acid (8.65 and 7.68%, respectively).

Table (2) : HPLC of Sugar Compositions of Gum Arabic

Sugar compounds	**g./100g.**
L-arabinose	37.54
L- rhamnose	8.65
D-glucuronic acid	7.68
D-galactose	41.37

Results are in accordance with the studies on the structure of gum arabic indicate that consisting the molecules of glucuronic acid and 4-*O*methyl- D-glucuronic acid[56-58].

Table (3) illustrates the fractionation of phenolic compounds in gum Arabic by HPLC. Results indicate that gum Arabic contains catechin as a predominant phenolic compound recording 442.14 mg/100g., followed by epicatechin and gallic acid (185.32 and 168.84 mg/100g., respectively).

Table (3) : HPLC of phenolic compounds of gum (mg/100g.)

Phenolic compounds	**(mg/100g.)**
Quinic acid	3.64
Tannic acid	11.42
Pyrogallol	91.36
Gallic acid	168.84
Catechein	442.14
Epicatechein	185.32
Catechol	67.42
3-methoxybenzoic acid	45.87
Caffeic acid	1.43
Vanillic acid	92.18
P-Coumaric acid	5.82
Benzoic acid	42.49
Salycilic acid	84.52
rosmarinic acid	10.63
-cinnamic acid	8.57
Coumarin	6.88
trans-Caffeic acid	2.39

Results are in agreement with those obtained by various studies involving catechin and epicatechin fractions from plants that have demonstrated antineoplastic [59], and anti-inflammatory properties [60].

Some recent reports have claimed that GA possesses antioxidant and nephroprotectant effects [2]. Gum arabic contains a high molecular weight (lipoprotein) heterogeneous gum polysaccharides [7].Furthermore, the aqueous extract of *A. catechu* has been shown to be a rich source of catechin and epicatechin. The anti-inflammatory, antineoplastic, and analgesic activities are all believed to be due to the antioxidant activities; being phenolic compounds [52].

Biological effects of administration of gum Arabic :

Results presented in **Fig. (1)** reveal the effect of administration of gum arabic extracts (5, 10 or 15%) to diabetic rats and to chronic kidney disease (CKD) rats on serum glucose (mg/dl). Diabetic rats suffers from high serum glucose level recording 361.806 mg/dl. Concerning diabetic rats fed on gum Arabic solutions at concentrations of 5, 10 and 15% on serum glucose, it decreased gradually due to administration of gum Arabic at the aforementioned concentrations, respectively.

Results agree with [61]who reported that **t**he fasting blood glucose was decreased by treatment with GA as compared to non-treated mice.

Moreover, chronic kidney disease (CKD) rats had normal levels of serum glucose. In concern to chronic kidney disease rats fed on the aforementioned concentrations of gum Arabic, in general, results show that administration of gum Arabic by all concentrations used causing slight decrease in serum glucose, nearly around the normal.

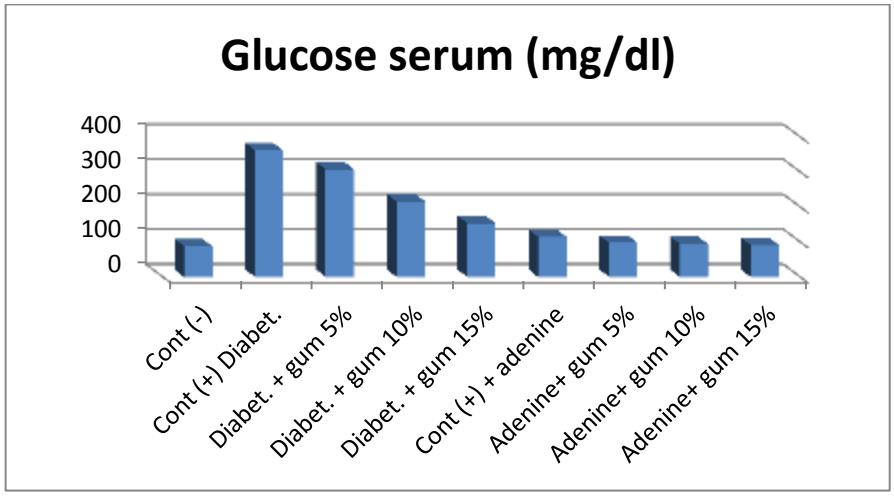
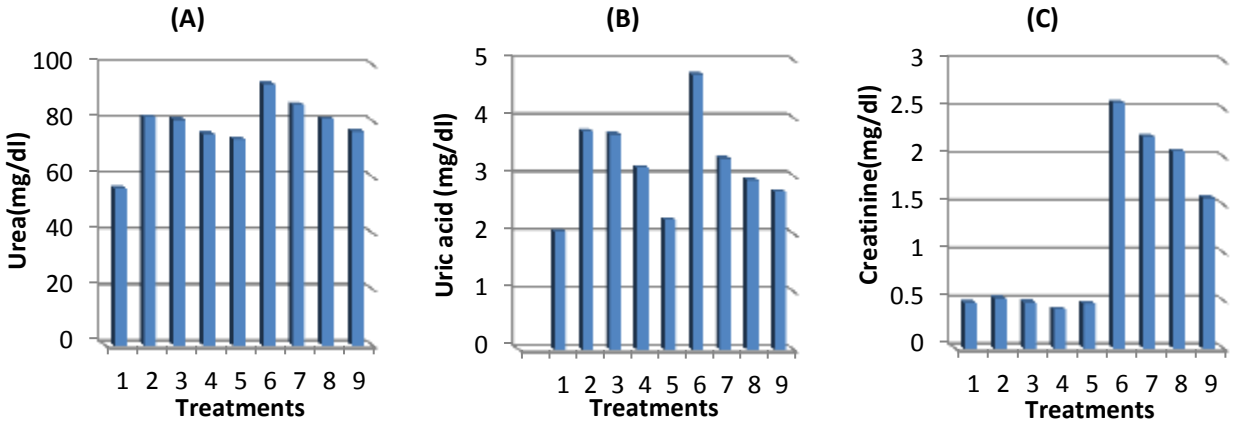


Fig. (1) : Effect of administration of gum Arabic to diabetic or CKD rats on Glucose serum (mg/dl)

Results are in agreement with those reported by [31]who stated that GA inhibits intestinal glucose absorption by down-regulation of the membrane abundance of SGLT1 which is the major route for intestinal glucose absorption. Moreover, [32] also reported that GA treatment significantly reduced urinary glucose excretion, Na+ excretion and urinary volume. Diabetic mice suffered from albuminuria, which was significantly decreased by GA treatment.

Hyperglycemia can cause oxidative stress, which in turn, may result in cellular tissue damage. The harmful influence of diabetes on metabolism of tissues and organs is well known. Likewise, uncontrolled hyperglycemia can lead to disturbances in the structure and function of organs [62].

Figs (2A, B and C) illustrate the effect of administration of gum Arabic extracts (5, 10 and 15%) on diabetic or chronic kidney disease rats. Diabetic rats suffers from high levels of urea (2A), uric acid (2B), and creatinine (2C). As for diabetic rats fed on gum Arabic extracts(5, 10 and 15%), it is obvious that gum Arabic caused to decrease uric acid. The best treatment was using 15% GA recording the least uric acid value (2.246 mg/dl) compared to positive control (3.778mg/dl). Also, both serum urea and creatinine had the same trend due to administration of GA gradually by the concentrations of 5, 10 and 15%, respectively. Generally, kidney function was still on normal basis due to either diabetes or to administration of GA.



Treatments:1- control(-), 2- control(+), 3- diabet. + 5% gum Arabic, 4- diabet. + 10% gum Arabic, 5- diabet. +15% gum Arabic, 6- control(+) + adenine, 7- adenine + 5% gum Arabic, 8- adenine + 10% gum Arabic, 9- adenine + 15% gum Arabic.

Figs (2) : Effect of administration of gum Arabic to diabetic or CKD rats on Kidney function (serum Urea (2A), serum Uric acid (2B) and serum Creatinine (2C) (mg/dl))

On the other side, CKD rats suffers from high levels ofurea, uric acid and creatinine. Concerning the effect of administration of gum Arabic (5, 10and 15%) on chronic kidney disease rats, it is clear that gum Arabic feeding caused decreases in urea from 93.188 to 76.22, uric acid serum from 4.756 to 2.728 and creatinine for 2.562 to 1.568 mg/dl at 15% gum Arabic, respectively.

These results are in accordance with those obtained by [63]who mentioned that in chronic renal failure (CRF) patients, serum urea nitrogen was significantly decreased during supplementation with gum. Furthermore; clinically, [64]claimed that GA helps to reduce urea and creatinine plasma concentrations and reduces the need for dialysis from 3 to 2 timesper week in chronic renal failure patients.

Also, Similar results of urea-lowering effect of GA by increasing urea nitrogen (N)excretion in stools, with a decrease in the total Nexcreted in urine was discussed by [65-66].

Results in**Table (4)**illustrates the effect of administration of GA extracts (5, 10 and 15%) on diabetic and chronic kidney disease (CKD) rats antioxidant enzymes.Diabetic rats suffers from low glutathione peroxidase, superoxide dismutase and catalase levels. Concerning the administration of GA on diabetic rats, it is clear the antioxidant enzymes revealed remarkable increases in glutathione peroxidase, superoxide dismutase and catalase due to using GA recording 14.302, 16.206 and 17.820 for glutathione; 2.738, 3.198 and 3.600 for SOD and 29.028, 34.026 and 50.260 for catalase, respectively for 5, 10 and 15% GA.

Table (4) : Effect of administration of gum Arabic to diabetic or CKD rats on Oxidative enzymes (Glutathione, superoxide dismutase and catalase)

Treatment	**Glutathione (IU/mg protein)**	**Superoxide dismutase (SOD) (IU/mg protein)**	**Catalase (IU/mg protein)**
Cont (-)	18.452	3.824	51.816
Cont (+) Diabet.	11.688	2.202	25.944
Diabet. + gum 5%	14.302	2.738	29.028
Diabet. + gum 10%	16.206	3.198	34.026
Diabet. +gum 15%	17.820	3.600	50.260
Cont (+) +adenine	11.300	2.328	20.694
Adenine+gum 5%	13.688	2.622	23.880
Adenine+gum 10%	15.104	2.960	35.190
Adenine+gum 15%	15.952	3.500	42.102
L.S.D. at 5%	***0.868***	*0.365*	*3.354*

However, CKD rats suffer from low levels of antioxidant enzymes (glutathione peroxidase, superoxide dismutase and catalase). Concerning chronic kidney disease (CKD) rats fed on GA solutions (5, 10 and 15%), it could be noticed that GA enhanced glutathione peroxidase, superoxide dismutase and catalase due to using GA. It recorded 13.688, 15.104 and 15.952 for glutathione; 2.622, 2.960 and 3.500 for SOD and 23.880, 35.190 and 42.102 for catalase, respectively by 5, 10 and 15%.

The activities of superoxide dismutase (SOD), catalase (CAT)and glutathione peroxidase (GPX) constitute a first line antioxidant defense system which plays a key and fundamental role in the total defense mechanisms and strategies in biological systems. Superoxide dismutase (SOD) is the first detoxification enzyme and most powerful antioxidant in the cell. It is an important endogenous antioxidant enzyme that acts as a component of firstline defense system against reactive oxygen species (ROS)[67-68].

Results agree with those who investigated antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidases, glutathione reductases and glutathione-s-transferases for the prevention and treatment of diseases resulting from oxidative damage[69-72].

Some recent reports have claimed that GA possesses antioxidant and nephroprotectant effects[2].

Mechanistically, the extracts of *A. catechu* has been shown to enhance various antioxidant enzymes, increase cellular content of reduced glutathione, which is one of the primary endogenous antioxidants, and inhibit lipid peroxidation and DNA damage[73].

GA is a potent superoxide scavenger [74] so that it give protective effect against both acetaminophen-induced hepatotoxicity [75] and doxorubicin-induced cardiotoxicity in mices [74].

Evidence suggests that impaired antioxidant status is involved in oxidative stress associated with diabetes. Antioxidant therapy in the diabetic rats normalized Cu, Zn, SOD and GPX protein expression[76].

Table (5)demonstrates the effect of administration of gum Arabic extracts (5, 10 and 15%) on diabetic and chronic kidney disease (CKD) rats body and kidney weights. Diabetic rats suffer from low body weight and kidney weight levels. Concerning the administration of GA on diabetic rats, it is clear that an enhancement in body weight and kidney weight has been caused due to the administration of GA.

On the other hand, CKD rats suffer from low levels of body and kidney weights. Concerning chronic kidney disease (CKD) rats fed on GA extracts (5, 10 and 15%), it could be noticed that GA had no significant effect on both body and kidney weights, as it fluctuated up and down due to the administration of GA to CKD rats.

Table (5) : Effect of administration of gum Arabic to diabetic or CKD rats on Body weight and weight of kidney (g.)

Treatment	**Body weight (g.)**	**Weight of Kidney (g.)**
Cont (-)	324.0	2.09640
Cont (+) Diabet.	296.4	1.69000
Diabet. + gum 5%	300.0	1.74600
Diabet. + gum 10%	306.2	1.81740
Diabet. +gum 15%	307.4	1.91120
Cont (+) +adenine	313.2	3.97240
Adenine+gum 5%	312.6	2.48080
Adenine+gum 10%	313.8	3.12042
Adenine+gum 15%	314.4	3.06700
L.S.D. at 5%	***10.903***	***0.169***

Results agree with the fact that diabetic animals showed marked weight loss[76]. [77]showed that drinking the GA supplemented *ad libitum* showed accelerated recovery in comparison to those receiving either water or without gum. Recovery parameters included greater enhancement of weight gain, food and fluid intake, and a lower fecal output in rats who's contained GA.

Conclusion

From this study, it could be recommended that using GA aqueous extract as natural source of antioxidants serve as a food supplement in enhancing the diabetic and/or chronic kidney disease patients health thus decrease complications of diabetes and CKD patients.

From another point of view, GA has an obvious effect as a natural antioxidant in curing patients from oxidative stress caused from diabetes and chronic kidney disease due to enhancing antioxidant enzymes (GPx, SOD and Cat) which represent the first antioxidant line defense system playing a key role in the total defense mechanisms in biological systems. This can cause the serum glucose levels and kidney function to be enhanced.

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