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RESEARCH ARTICLE – GENERAL BIOCHEMISTRY, GENETIC AND MOLECULAR BIOLOGY

The Effect of Ginkgo Biloba Extract on Mice Treated with Taxol

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Abstract

Background: The Ginkgo biloba plant is the sole extant species of the Ginkgoaceae family and is among the oldest seed plants. The extract of Ginkgo biloba leaves can also augment the activities of antioxidant enzymes, including both enzymatic and nonenzymatic systems. Antioxidant enzymes comprise catalase, superoxide.

Objective of study: Thirty-six albino mice, sourced from Babylon University and weighing 30±5 grams, were utilized in this study. Water and processed dry food were provided. The animals were categorized into six groups, with six mice per group, and maintained under standardized circumstances (25°C, 12-hour light/12-hour dark cycle).

Materials and Methods: In this study, 100 pregnant women—50 PCS sufferers and 50 stable controls—were assessed for functional polymorphisms of the TGFB1 gene [C-509 T]. Heterozygous CT accounted for 24% of PCS patients and 30% of controls, whereas homozygous CC accounted for 76% of PCS cases and 70% of normal, healthy pregnant women.

Results: Our phytochemical analysis of methanol-aqueous Ginkgo biloba leaf extracts revealed the presence of essential oils, alkaloids, flavonoid glycosides, tannins, phenolic compounds, saponins, coumarins, and terpenes. In contrast, steroids and resin exhibited poor results.

Conclusion: This study showed that Taxol (6 mg/kg b.wt.) generated cytotoxicity and genotoxicity in the liver and spleen; however, these adverse effects may be mitigated or even prevented in certain instances by the protective effect.

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Keywords: Ginkgo Biloba, Mice, Taxol, Diabetes Mellitus, Cancer.

1. Introduction

As the only living member of the Ginkgoaceae family, the ginkgo biloba is one of the oldest seed plants and is frequently referred to as a "living fossil" because of its early Jurassic origins According to evolutionary assessments of ancient leaves and reproductive parts, Ginkgo biloba's morphology hasn't changed much in the last 100 million years. The name ginkgo biloba comes from the Chinese terms sankyo or yin-kuo, which indicate hill apricot or silver fruit. The term ginkgo biloba comes from the Chinese words sankyo or yin-kuo. The mature, apricot-shaped, golden fruits of the ginkgo biloba tree are produced. Ginkgo biloba grows to a height of around 40 meters, demonstrating moderate growth. This plant is deciduous, with green leaves that turn golden in the fall. Simple fan-shaped leaves with lobed margins and alternating arrangement are 3–5inches (5–10 cm) long and have parallel venation. Inedible, foul-smelling fruit with a hard, edible core is produced by female ginkgo biloba plants [1,2,3].

The antioxidant properties of the flavonoid include both direct scavenging of free radicals and indirect inhibition of their formation [4]. Reactive oxygen species (ROS) can be eliminated by ginkgo leaf extract. Superoxide (O2), hydroxyl radicals (HO), lipid hydroperoxides, hydrogen peroxide (H2O2), hypochlorous acid (HOCl), nitric oxide (NO), and)NO2) are all considered reactive oxygen species (ROS). Additionally, the enzymatic and nonenzymatic systems of antioxidant enzymes can be enhanced by the extract of Ginkgo biloba leaves. Catalase, glutathione peroxidase, and superoxide dismutase are examples of antioxidant enzymes [5]. It is known that ginkgo biloba extract is an antioxidant that prevents the formation of tumors [6]. The Pacific yew tree's bark was the original source of the anticancer medication taxol. It is Direct interactions between cytotoxic medications and DNA or its precursors prevent the synthesis of new genetic material or damage DNA irreversibly, which results in apoptosis. The inability of cytotoxic medications to differentiate between cancerous and healthy cells is one of the biggest issues. Cancer cells can produce large amounts of hydrogen peroxide (H2O2) and cause antioxidant imbalances, which may help them mutate and invade healthy tissues, causing damage. Glycosides have a major role in preventing the growth of tumors. Flavonoids have the ability to counteract hydroxyl and superoxide radicals and stop the chain reactions that lead to lipid peroxidation. Ginkgo biloba is used to treat a number of conditions, such as diabetes, asthma, cardiovascular protection, hepatoprotection, and important central nervous system activities, according to numerous research [7, 8, 9].

2. Materials and Methods

2.1. Plant extraction and preparation

The preparation of plant extracts was done by extracting approximately 750 grams of powdered material with a 20% methanol to 80% distilled water mixture (V/V), employing an average ratio of 1 gram of plant powder to 3 grams of the solvent mixture, and blending for 30 minutes at ambient temperature. The suspension was strained through gauze, and the concentrated filtrate was thereafter heated in an oven at 45 ℃ until dehydrated. The dehydrated crude extracts were stored at 4 ℃ until use. The details in table 1 shown detection of Some phytochemical compounds in the *ginkgo biloba* leaves extract in the results to use in next step.

2.2. Experimental animals

Housing of the animal include thirty-six albino mice, 30±5 grams, were utilized in this study, sourced from Babylon University. Water and processed dry food were provided. The animals were categorized into six groups, each including six mice, and maintained under standardized circumstances (25℃, 12-hour light/12-hour dark cycle).

2.3. Groups of animals under investigation

Six groups of mice, each with six animals, were randomly selected. The untreated control was group 1 and group 2 was given 500 mg/kg of ginkgo biloba extract orally. Group 3 received an intraperitoneal injection of 6 mg/kg of Taxol. Group 4 got both taxol (6 mg/kg, i.p.) and ginkgo biloba (500 mg/kg, oral) at the same time. Ginkgo biloba (500 mg/kg, oral) and Taxol (6 mg/kg, i.p.) were administered to Group 5 after 24 hours. Taxol (6 mg/kg, i.p.) was administered to Group 6 first, and then, 24 hours later, Ginkgo biloba (500 mg/kg, oral).

2.4. Total genomic DNA extraction

Genomic DNA from white blood cells (WBCs) for both mice was extracted using a DNA extraction kit (Favorgen) according to the leaflet of the kit; Special protocol frozen Blood as a manufacturer company.

2.5. DNA fragmentation and apoptosis analysis

Gel preparation for the detection of the DNA extract include electrophoretic-grade agarose (BRL) at a concentration of 1.5% was used to create gels. then given an hour to solidify at ambient temperature. A digital camera was used to take pictures of the gel after DNA electrophoresis was completed with 1× TBE running buffer for 1.5 hours. A 312 nm UV laser was used to visualize the DNA from WBCs for each mouse in the various groups. DNA fragmentation: - 180, 360, 540, and 720 bp apoptotic bands of DNA fragmentation, in contrast to a 14-band DNA marker (100–3000 bp, Fermentas). ImageJ software was used to quantify band intensity based on optical density.

Examination of chromosomal abnormalities and the mitotic index in mouse somatic cells to stop the animals at metaphase, 0.5 ml (0.0012%) colchicine (3 mg/kg body weight) was administered to them two hours prior to sacrifice. After being extracted in an isotonic NaCl solution (0.9%), the bone marrow was incubated in 0.56% KCl for 20 minutes at 37ºC. Methanol and glacial acetic acid (3:1) are added dropwise to create the fixation, and after 10 minutes, centrifugation is carried out. Repeat three times with the pellet. In accordance with the procedure (Preston et al.), the pellet was resuspended in fix solution and dropped from high space onto a cold slide that had been dipped in cold 70% ethyl alcohol. It was then allowed to air dry and stained after 24 hours. 100 metaphase spreads were evaluated for chromosomal abnormalities for every animal. The mitotic index (MI), which was determined using this formula, required the counting of at least 500 cells. DNA fragmentation include 180 bp and its multiples 360, 540, and 720 bp, apoptotic bands of DNA fragmentation appeared in contrast to the fourteen bands of the DNA marker (100–3000 bp, Fermentas). The intensity of the apoptotic bands could be measured using optical density data in the ImageJ application.

3. Statistical analysis

Means and standard deviations (SD) were computed for descriptive statistical documentation utilizing sigma plot exact graphs and data analysis software. The significance of the difference was assessed using Student's t-test.

4. Results

Our phytochemical detection results of methanol-aqueous ginkgo biloba leaf extracts revealed the presence of essential oil alkaloid, flavonoid glycosides, tannins, phenol compounds, saponin, coumarins, and terpenes. Whereas steroid and resin showed negative detection as shown in table 1. The majority of aberrations for all experimental groups were chromatid breaks, aneuploidy, fragmented chromosomes, ring chromosomes, polyploid chromosomes, and elongated chromosomes, as shown in Fig. 1.

The Taxol increase chromosome aberration in bone marrow cell to 53.11% Compared to the control show 5.65 treatment with 500 mg\kg of plant extract reduce aberration significantly ($P \leq 0.05$) to 1.61% and 2.59% pre-treatment with Taxol follow by plant show no significant change (45.98%) where the combination of Taxol and ginkgo biloba treatment reduce aberration to 1.61% as compared with the normal control group.

Table .1. Detection of some phytochemical compounds in the *ginkgo biloba* leaves extract

Phytochemical Compound	Detection Method		G.Biloba Leaves Extract
	Reagent	Positive Result	
Alkaloids	Wagner	Brown Color	+
Essential Oil	I-v Light	Orange Color	+
Phenols Compound	Ferric Chloride	Yellow Color	+
Glycosides	Benedict	Red Pellet	+
Flavonoids	Ethanol (50%) –KOH (50%) (1:1)	Yellow Color	+
saponins	Shaken	Formation of Foam	+
Terpenes	Chloroform + Acetic Acid+ 112SO4	Blue Color	+
coumarins	1.-N- Light	Bright Pink Color	+
tannins	Lead Acetate 1%	White Gelati Pellet	+
Resin	HCl 4%	Turbidity	_
Steroids	Chloroform +Acetic Acid+H:SO4		_

Note: Mitotic index (%) = (Metaphase) X 100 / (resting cells + prophase + metaphase)
*(+) indicate positive result *(-) indicate negative result

Table 2. The mean changes (mean ± S.E) in some chromosomal aberrations of experimental mice bone marrow cells

Group	Chromatid break%	Chromosome break%	Aneuploidy %	Polyploidy %	Analytic %	Fragment %	Ring Chromosome %	Sum
control	0.33±9.67	1.52±7.00	1.76±5.33	1.52±3.00	0	0.66±0.06	2.00±4.00	5.65
Tax&(6 mg/kg) for 24h	110.0±5.77	83.33±1.66	82.33±1.45	112.00±1.15	2.66±2.66	54.33±4.33	86.66+3.33	53.11
G.B.E (500mg/kg) for 24h	6.00±2.00	2.00±0.00	8.33±0.33	2.33±0.33	5.66±1.45	7.00±1.52	7.33±0.66	3.82
Taxol 6mg/kg for 24 hr followed by G.B.E conc. (500mg/kg) for 24h	83.33±12.01	26.00±2.00	133.32±133.3	1.33±0.66	148.33±56.7	80.01±11.45	11.34±4.66	45.98
(G.B.E)(500mg/kg) for 24 h followed by faxol(6mg/kg) 24h	4.00±1.52	1.0±0.00	6.33±0.33	2.00±11.00	3.66±1. 33	5.00±2.00	4.00±1.00	2.59
In xol(6mg/kg)+G.B.E (500mg/kg)for 24h	3.05±1.15	0.33±0.33	4.02±0.57	1.33±10.88	2.66±1.33	2.60±1.33	2.34±0.66	1.61

Similar letters indicate a non-significant difference (n=6 (number of groups) for each group), while different letters indicate a significant difference ($P \leq 0.05$) between groups when compared to the Taxol group. Standard Error, or S.E.

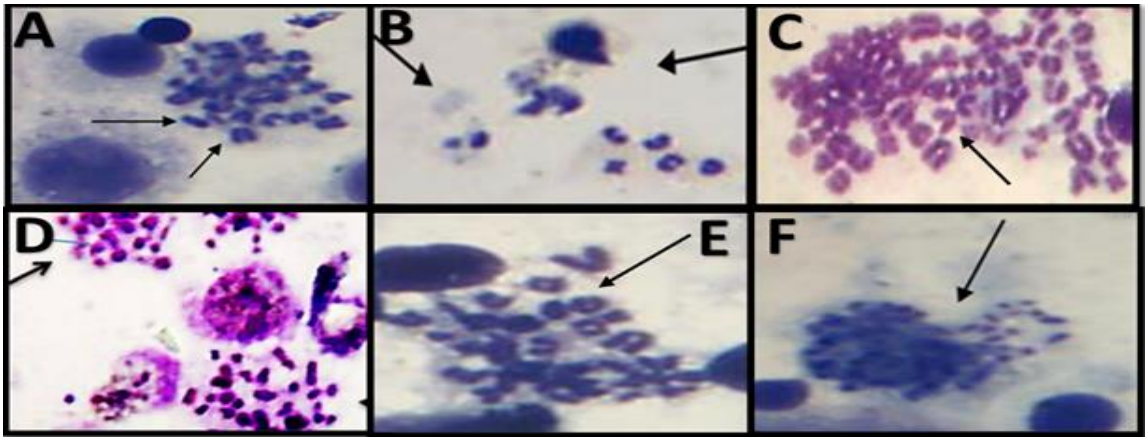

Fig. 1. Showing the differences in types of chromosomal aberrations for all experimental groups **(A)** chromosome and chromatid breaks, (B) aneuploidy, (C) polyploid, (D) Analytic, (E) ring chromosomes, and (F) Fragmented chromosomes in metaphase of mice bone marrow cells (Giemsa stain, 1000X)

Table 3 Shows a significant decrease in mitotic index (MI) in the Taxol group (1.40 ± 0.49) compared to the control (5.06 ± 0.57) and ginkgo biloba group (5.53 ± 0.49). pre-treatment with ginkgo biloba (500 mg/kg) followed by Taxol increase MI significantly (6.06 ± 0.43), while simultaneous treatment and post -Taxol Ginkgo Biloba treatment showed MI treatment value of 1.73 ± 0.83 and 1.56 ± 0.44, respectively- both significantly different from the Taxol group.

Table 3. Mitotic index of experimental mice (mean ± S.E)

Group	Mitotic index (MI)
Control	(5.06±0.57) *
Taxol (6 mg/kg) for 24h	(1.40±0.49) #
G.B.E (500mg/kg) for 24h	(5.53±0.49) *
Taxol 6mg/kg for 24 hr followed by G.B.E conc. (500mg/kg) for 24h	(1.56±0.44) *#
(G.B.E) (500mg/kg) for 24 h followed by Taxol (6mg/kg) 24h	(1.73±0.83) #
Taxol (6mg/kg) G.B. E (500mg/kg) for 24h	(6.06±0.43) *#

*****# refers to a significant difference (P ≤ 0.05) between groups with respect to the Taxol group. Similar letters refer to a non-significant difference DNA fragmentation analysis, as shown in Figure 2 and Table 4, revealed a smearing pattern on the agarose gel. In the Taxol group, the smear appeared at ~9300 bp with a size range of 0,000–700 bp in mice treated with 500 mg\kg Ginkgo biloba extract 24h after 6 mg/kg Taxol showed fragmentation at ~4000 bp (10,000–6000 bp). No fragmentation is observed in the control or the group receiving ginkgo biloba simultaneously with intact DNA around 10,000 bp. Pre-treatment with Ginkgo biloba before Taxol showed fragmentation at ~2000 bp with the size range of 10,000–8000 bp.

Table 4. DNA fragmented level in white blood cell extraction compared to normal control

Lane no.	Group	Base pair of the band	fragmented level as compared to normal control
1	DNA marker	10000	-
2	control	10000-10000	-
3	G.B.E(500mg/kg) for 24h	10000-10000	-
4	Taxol (6 mg/kg) for 24h	10000-700	9300
5	Taxol 6mg/kg for 24 hrfollowed by G.B.E cone. (500mg/kg)for 24h	10000-8000	2000
6	(G.B.E) (500mg/kg)for 24 h followedby Taxol (6mg/kg) 24h	10000-6000	4000
7	Taxol (6mg/kg) + G.B.E (500mg/kg) for 24h	10000-10000	-

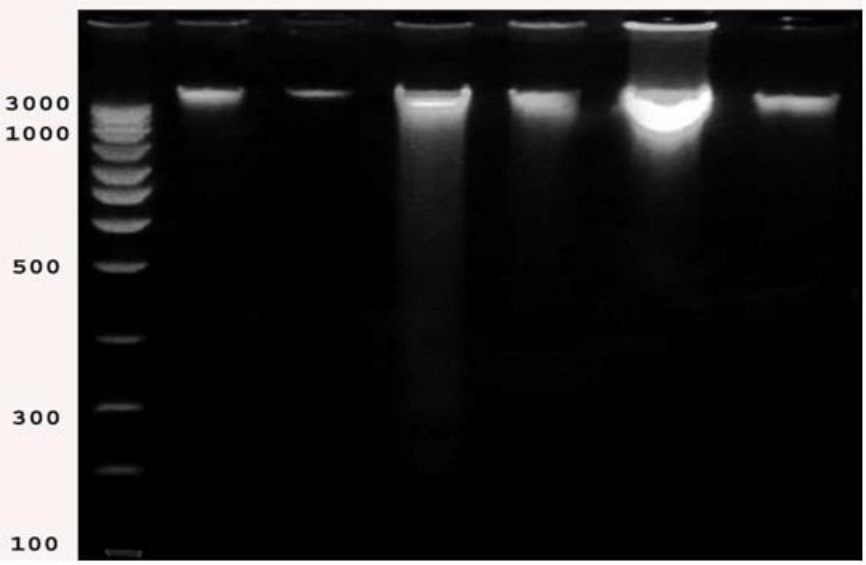

Fig. 2. Electrophoresis of DNA extracted from the blood of experimental cohorts. M: DNA ladder (1 kb); lane 1: control; lane 2: plant extract (500 mg/kg); lane 3: Taxol (6 mg/kg); lane 4: Taxol (6 mg/kg) administered for 24 hours, followed by G.B.E. (500 mg/kg) for 24 hours; lane 5: G.B.E. (500 mg/kg) for 24 hours, followed by Taxol (6 mg/kg) for 24 hours; lane 6: concurrent administration of Taxol (6 mg/kg) and G.B.E. (500 mg/kg).

5. Discussion

Numerous detection approaches utilize bioactive chemicals from plant extracts, indicating that the methanol-water extract of Ginkgo biloba contains alkaloids, essential oils, phenolic compounds, glycosides, flavonoids, saponins, terpenes, coumarins, and tannins. Numerous studies have documented the existence of various groups of constituents in Ginkgo biloba extract. The findings pertain to additional research indicating that the chemical analysis of crude Ginkgo biloba extract includes flavanol glycosides. [10,11,12]. Several studies have shown that ginkgo biloba extract contains terpenoids, polyphenols, organic acids, carbohydrates, essential fatty acids, inorganic salts, and amino acids [13,14]. Terpenoid lactones, ginkgolides, ginkgolide A, ginkgolide B, ginkgolide C, and bilobalide are among the phytochemical compounds that have demonstrated inhibitory effects on tumor mutations and the prevention of multistage carcinogenesis [15]. The results indicated a substantial degree of fragmentation in the Taxol group. Inhibited mitosis and normal cell division lead to apoptosis because of the drug's ability to disrupt a cell's microtubule function by stabilizing microtubule formation [16]. The damage was reduced by approximately 7300 bp in the groups that received 6 mg/kg of Taxol before and after receiving 500 mg/kg of plant. The group that received Taxol before the plant experienced a fragment of 2000 bp, while the group that received Taxol after the plant experienced a fragment of 4000 bp.

The preventive action of ginkgo biloba, an antioxidant plant that contains active chemical constituents such as flavonoids (flavones, flavonols, tannins, and bi-flavones), may be the cause of these outcomes. Terpenoids that function as platelet activation factor antagonists and can lower platelet activation and aggregation, which enhances blood circulation, as well as quercetin glucosides and kaempferol, which are antioxidants and free radical scavengers, enzyme inhibitors, and cation chelating agents. Removal of pollutants from the body, including oxidative [17,18] examined the leaf extract of ginkgo biloba. Antioxidant herbal medication decreased the production of reactive oxygen species (ROS) and the expression of inflammatory proteins in human vascular endothelial cells induced by oxidized low-density lipoprotein. Additionally, ginkgo biloba helps guard against oxidative stress, neuronal DNA damage, and memory impairment brought on by intermittent hypoxia. Normal DNA bands were seen in the group that got both plant and Taxol. These findings are associated with ginkgo biloba's antioxidant activity, which lowers or stops the production of free radicals to preserve genomic integrity or enhance the DNA repair system's capacity.
A genotoxicity test called the chromosomal aberration test is used to identify DNA damage and cause structural alterations in chromosomes. Intra-chromosome (inside one chromosome, such as terminal or interstitial detection and inversion) and inter-chromosomal (between two or more chromosomes, such as translocation and dicentrics) aberrations are categorized. [19].

The findings suggest that, in comparison to the control and the plant, the frequency of chromosomal abnormalities in the bone marrow cells of the Taxol group has significantly increased. The toxicity of the cell increases as a result of the accumulation of oxidative stress and the elevation of chromosomal abnormalities linked to the effects of Taxol. [20,21] examined the genotoxicity effect of the anti-cancer medication Taxol on chromosomal abnormalities and discovered that the drug's ability to block microtubule dynamics against cancer cells caused a considerable rise in chromosomal abnormalities after treatment [22]. A single intraperitoneal injection of Taxol has mild mitogenic, mutagenic, and apoptogenic effects, as well as inducing thrombocytopenia, neutropenia, moderate hypoplastic anemia, and reversible bone marrow hypoplasia. Furthermore, the groups that received Ginkgo biloba + Taxol demonstrated a significant reduction in all types of aberrations as compared to the Taxol group. Additionally, compared to the group that took ginkgo biloba prior to receiving Taxol (11.34%), there were fewer bone marrow cells with chromosomal abnormalities (2.34%). This may be due to the phytochemicals—alkaloids, flavonoids, terpenoids, saponins, tannins, glycosides, protein, acidic compounds, and carbohydrates—that are present in the ginkgo biloba leaf extract. and tannins are substances that have antioxidant properties [23, 24]. Research on Ginkgo biloba's protective effect on chromosomal abnormalities in rats revealed that it reduces chromosomal aberrations through antioxidant activity. Flavone glycosides and terpene lactones, which scavenge free radicals and boost the activity of antioxidant enzymes, are two components of ginkgo biloba extract that contribute to its pharmacological effects. The mitotic index

test is a cytogenic assay that measures cell proliferation directly, evaluates the genotoxic and mutagenic effects of drugs, and identifies substances that either block or promote mitotic progression. It has been used as a prognostic indicator in a number of human cancers. [25, 26, 27]. The Taxol reduces depolymerization and disrupts the development of the mitotic spindle, preventing the cells from completing a normal mitosis (mitotic arrest) [28,29]. After receiving injections of Taxol for 24 and 48 hours, bone marrow cells' mitotic index values significantly decreased, with all doses being compared to the control group. Taxol's effect on microtubule assembly and stability, which further impairs regeneration processes essential for sustaining cellular activity in the presence of hazardous chemicals, was the explanation for this [30,31]. But the group that received treatment The notable improvement in mitotic index (5 53±0.49) observed with a dose of 500 mg/kg of plant after Several representative constituents, including flavonoids [32,33], terpene trilactones, terpenoids, polyphenols, phenol, organic acids, carbohydrates, fatty acids and lipids [34], inorganic salts, and amino acids, which function as antioxidants, free radical scavengers, and action chelators [35], may be responsible for Taxol. Finally, studies using animal models have suggested that they may offer protection against certain types of cancer [36,37].

6. Conclusion

In this study, Taxol (6mg/kg b.wt.) induced cytotoxicity and genotoxicity in liver and spleen, but these side effects can be reduced or even prevented in some cases by the protective effect of plant origin, such as Ginkgo biloba, at the dose of 500 mg/kg b.wt. The Taxol group's mitotic index (MI) was significantly lower than that of the normal control group, according to the MI data. Taxol's method of action, which stabilizes microtubules and dampens polymer dynamics, may be the cause of this outcome.

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Nomenclature & Symbols			
ROS	GBE	*Ginkgo biloba* Extract	Tumor Necrosis Factor-alpha
SD	standard deviations	WBCs	white blood cells
NO	nitric oxide	DNA	Deoxyribonucleic acid
MI	mitotic index	SE	Standard Error

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