doi.org/10.36721/PJPS.2024.37.3.REG.705-713.1

Clinical efficacy and mechanism of *Ginkgo biloba* extract in the treatment of elderly ischemic cerebrovascular disease

Qiuhong Zhu and Dilongtian Liu
Department of Neurology, Wuhan Wuchang Hospital, No. 116 Yangyuan Street, Wuchang District, Wuhan, Hubei, China

Abstract: The investigation's aim was to explore the medical usefulness and mechanism of GBE in the management of elderly ischemic cerebrovascular disease (ICVD).120 cases of elderly patients with ICVD admitted to our hospital from August 2022 to August 2023 were chosen as participants for this research and the sufferer were allocated to the conventional (60 cases) and GBE group (60 cases) using the method of randomized number. NIHSS score, Barthel index, hemodynamic indexes, serum inflammatory factor levels, platelet-activating factor (PAF) and clinical efficacy were recorded before(T0) and after treatment(T1),and recorded the adverse reactions of the two groups during the treatment. At T1, NIHSS score, WBLSV, PV, HCT, TNF-α, IL-6 and PAF in the two groups, which were all notably reduced compared to T0, and the Barthel index demonstrated a significant increase compared to its T0 value ($P<0.05$). At T1, GBE group exhibited notably reductions in NIHSS score, WBLSV, PV, HCT, TNF-α, IL-6 and PAF compared to conventional group, whereas Barthel index and the total effective rate were considerably elevated ($P<0.05$). Incidence of adverse reactions were similar in both groups ($P>0.05$).GBE has good therapeutic benefits in managing elderly ICVD, effectively facilitate the recuperation of patients' neurological function, has obvious anti-inflammatory effect, improves patients' cerebral circulation and hemorheology indexes and makes the patients' daily life ability significantly improved, which has a good clinical application value.

Keywords: *Ginkgo biloba* extract, elderly ischemic cerebrovascular disease, clinical efficacy, mechanism.

INTRODUCTION

Ischemic cerebrovascular disease (ICVD) is a cerebrovascular blood supply disorder caused by a variety of etiological factors, and is commonly found in the elderly population. As the population ages, the incidence of ICVD in the elderly has been on a steady rise every year, making it one of the leading health conditions that pose a threat to the well-being and quality of life among the geriatric population (Tang *et al.*, 2019). In recent years, endovascular therapies for ICVD have been rapidly developed, such as the treatment of mechanical thrombus extraction for ICVD, which has allowed numerous patients to receive better treatment (Lin *et al.*, 2020). However, elderly patients usually have poorer physical function and recovery ability and may be accompanied by multiple chronic diseases and dysfunctions, which makes them less tolerant to high-risk procedures such as mechanical thrombolysis, which has limited therapeutic effects on the disease, and thus mechanical thrombolysis is generally not used (Deguchi *et al.*, 2022). Therefore, finding effective treatments is important to enhance the prognosis of elderly individuals suffering from ICVD.

In Chinese medicine theory, ischemic cerebrovascular disease is usually categorized as "stroke". According to Chinese medicine, this disease occurs when the qi and blood in the body are in disarray, resulting in the formation of blood stasis and blockage of cerebral vessels, thus affecting the normal function of the brain. Traditional Chinese medicine has accumulated a wealth of experience in treating cerebrovascular disease, and the main principles of treatment are to activate blood circulation, eliminate blood stagnation, regulate qi and blood, activate meridian channels and collateral vessels (Zhang *et al.*, 2023, Li *et al.*, 2022). *Ginkgo biloba* has garnered significant attention due to its distinctive pharmacological effects and in recent years, more and more studies have shown that *Ginkgo biloba* extract (GBE) shows potential clinical value in the treatment of ICVD (Peng *et al.*, 2021, Zhu *et al.*, 2022). GBE is a substance isolated and extracted from the leaves of *Ginkgo biloba* and its main active components are components such as terpene lactones and flavonoids, which exhibit diverse biological activities such as antioxidant, anti-inflammatory and antiplatelet aggregation (Yin *et al.*, 2024). Relevant research has demonstrated that GBE can decrease platelet aggregation, anticoagulation, improve cerebral blood flow, lower blood viscosity and have neuroprotective effects; at the same time, GBE exhibits a range of pharmacological activities, of which the main cardiovascular and cerebral vascular diseases and the central nervous system has a better therapeutic effect (Singh *et al.*, 2019, Li *et al.*, 2019). However, although there have been some studies exploring curative effect of GBE in managing ICVD, its specific mechanism of action is still not completely clear. In addition, for elderly patients with ICVD, their physiological characteristics and pathological changes are different from those of young patients, so the medical usefulness and mechanism of GBE in the management of

**Corresponding authors:* e-mails: matian4543@163.com

elderly ICVD still need to be further explored. This study takes elderly patients with ICVD as the research object, aims to explore the clinical efficacy and mechanism of GBE in treating elderly ICVD and provides a theoretical foundation for the scientific use of clinical medication.

MATERIALS AND METHODS

General information

120 cases of elderly patients with ICVD admitted to our hospital from August 2022 to August 2023 were chosen as participants for this research and the sufferer were allocated to the conventional (60 cases) and GBE group (60 cases) using the method of randomized number. Additionally, the two groups exhibited no notable disparities in the general information, thus ensuring comparability (P>0.05) (table 1).

Inclusion criteria

(1) age ≥60 years; (2) ischemic cerebrovascular disease diagnosed by CT/MRI of the cranial region (3) all patients were first time sufferers (4) patients were fully informed and provided consent.

Exclusion criteria

(1) the presence of autoimmune diseases or infectious diseases (2) the presence of congenital brain diseases or other serious organic diseases; (3) allergic to the medications being treated in this study; (4) hemorrhagic cerebrovascular disease.

Randomization and blinding

This research adopts the random number table method and double blind method. SPSS 26.0 statistical software was used to generate a random number sequence corresponding to the number of subjects. The generated random number was corresponding to the subject number, and the subjects were randomly assigned to the conventional group and the GBE group. The results of random assignment were recorded in detail to ensure that the grouping of each subject could be accurately identified during the follow-up study. At the same time, *Ginkgo biloba* extract injection and conventional treatment drugs were separately packed into the same containers and were coded and labeled to ensure that researchers, subjects could not distinguish between them. According to the allocation results of the random number method, the prepared drugs (or conventional treatment drugs) were distributed to the corresponding subjects and the researchers who were not involved in the treatment and evaluation of the subjects were responsible for ensuring the implementation of blinding. Throughout the study, participants and investigators (including the statisticians) were unaware of treatment and group assignments.

Methods

Patients in the conventional group received routine treatment, including monitoring vital signs, reducing intracranial pressure, blood glucose control, anti-infective treatment, maintenance of water-electrolyte balance and other symptomatic treatments and aspirin enteric-coated tablets (manufacturer: Hunan Xinhui Pharmaceutical Co., Ltd., approval number: State Pharmaceutical License H14021593, specification: 50mg* 100 tablets) were given orally, 100mg/time, 2 times/d. In addition to the conventional treatment, the GBE group received *Ginkgo biloba* extract injection (manufacturer: Yuekang Pharmaceutical Group Co., Ltd, approval number: H20070226, specification: 5mL: 17.5mg) 70mg, dissolved in 250mL of 0.9% sodium chloride injection (manufacturer: Jiangxi Kelun Pharmaceutical Co. H10983064, specification: 250mL: 2.25 g) and slowly titrated intravenously once/d. All patients received treatment for 2 weeks.

GBE is a drug with therapeutic effects extracted from *Ginkgo biloba* using modern processes and methods, with ginkgo flavonoids, ginkgolides and bilobalide as the main components (Pu *et al.*, 2024). The clinical application of GBE is quite wide, involving dozens of diseases in multiple systems such as neurological, circulatory, metabolic, endocrine, etc., especially in the treatment of ICVD has achieved better clinical efficacy. Fig. 1 shows the natural plant medicine *Ginkgo biloba*. Fig. 2 shows the chemical structural formula of the main components in GBE.

Fig. 1: Chinese herbal medicine *Ginkgo biloba*

Observation indexes and determination criteria

Clinical efficacy, neurological function, hemodynamic indexes, serum inflammatory factor level, platelet activating factor and daily life ability were used as observation indexes to assess the clinical therapeutic

effect of GBE on patients with ICVD and all relevant indexes were collected at the time points before (T0) and after (T1) 14 days of treatment.

(1) General information of patients gathered, encompassing factors such as gender, age, BMI and time from onset to admission, presence of hypertension and hyperlipidemia. (2) Neurological function: Sufferers' neurological status was appraised utilizing the National Institute of Health stroke scale (NIHSS) (Kwah *et al.*, 2014).The NIHSS score spans from 0 to 42, with increasingly higher scores signifying a more pronounced neurologic deficit and a less favorable neurologic recovery. (3) Clinical efficacy: Refer to the NIHSS score. Judgment criteria: obvious effect: significant improvement of clinical symptoms, NIHSS score decreased by ≥90%; effective: Clinical symptoms improved, NIHSS score decreased by 30%-89%; ineffective: clinical symptoms didn't change apparently, NIHSS score decreased by <30%. Total effective rate = (obvious + effective)/total number of cases× 100%. (4) Daily living ability: Sufferers' ability to perform daily living activities was appraised using the Barthel Index (BI)(da Costa *et al.*, 2022). The BI from 0-100 points, scores that were higher suggest superior daily living capabilities among the patients. Daily living ability can be divided into four grades: a total score of 100 indicates that the patient demonstrates excellent autonomy in performing daily living activities, eliminating the necessity for assistance from others; 61-99 indicates that patient exhibits good capacity in performing daily living activities, with mild dysfunction, and is able to perform some of the daily living activities independently; 41-60 indicates that the patient has a moderate degree of dysfunction, and needs a lot of help in order to perform the activities of daily living; ≤40 indicates that patient ability was severe dysfunction, and most of the activities of daily living cannot be performed on their own.(5) Hemodynamic index: Whole blood low-shear viscosity (WBLSV), plasma viscosity (PV) and hematocrit (HCT) were detected in patients using a blood rheology analyzer.(6)Serum inflammatory factors and platelet-activating factors: For both groups, 4mL of fasting venous blood was taken at T0 and T1, centrifuged at 2500r/min for 5min, and the supernatant was removed and stored at -20℃ for later detection. The concentrations of Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and platelet activating factor (PAF) were measured using the enzyme-linked immunosorbent assay (ELISA). (7)The occurrence of adverse reactions such as nausea, gastrointestinal reactions and mild rash were recorded during the treatment.

ETHICAL APPROVAL

The research was approved by the Ethics Committee of Wuhan Wuchang Hospital (No.20210633).

STATISTICAL ANALYSIS

Data analysis was conducted using SPSS 26.0 statistical software. Data passed normality test was described by mean ± standard deviation and analyzed using t-test. Conversely, data didn't pass normality test was represented by interquartile spacing and analyzed with rank sum test. Enumeration data was represented by n[(%)] and comparisons were made using the χ^2 test. P<0.05 was considered statistically significant.

RESULTS

Comparison of neurological function and daily life ability scores

At T1, both groups exhibited significant decreases in NIHSS scores (Conventional group :95CI%: [7.313,8.820], P<0.05; GBE group: 95CI%: [12.499, 14.201], P<0.05) and significant increases in the Barthel index compared to their T0 values(Conventional group: 95CI%:[-17.969,-12.697],P<0.05; GBE group: 95CI%:[-29.302, -23.364], P<0.05). Notably, GBE group demonstrated lower NIHSS scores (95CI%:[4.318,5.716], P<0.05) and higher Barthel index than conventional group(95CI%:[-15.501,-8.666], P<0.05)(fig. 3).

Comparison of hemorheology indexes

At T1, both groups exhibited significant decreases in WBLSV (Conventional group: 95CI%:[2.020, 2.760], P<0.05; GBE group: 95CI%: [3.402, 4.308],P<0.05), PV (Conventional group: 95CI%: [0.464, 0.732], P<0.05; GBE group: 95CI%: [0.820,1.164], P<0.05) and HCT(Conventional group: 95CI%: [5.306, 8.531], P<0.05; GBE group: 95CI%: [8.103, 11.603], P<0.05) compared to their T0 levels. Notably, GBE group demonstrated lower WBLSV (95CI%: [1.530, 2.222]), PV (95CI%: [0.211, 0.558]) and HCT (95CI%: [2.310, 6.494]) than conventional group(P<0.05) (fig. 4).

Comparison of serum inflammatory factors and PAF levels

At T1, both groups exhibited significant decreases in TNF-α (Conventional group: 95CI%: [0.204, 0.261], P<0.05; GBE group: 95CI%: [0.321, 0.391] , P<0.05) , IL-6 (Conventional group: 95CI%:[8.067, 9.949], P<0.05; GBE group: 95CI%: [12.591, 14.528], P<0.05) and PAF levels (Conventional group: 95CI%:[134.680, 175.940], P<0.05; GBE group: 95CI%: [178.553, 222.273], P<0.05) compared to their T0 levels. Notably, GBE group exhibited lower levels of TNF-α (95CI%:[0.090, 0.127]), IL-6 (95CI%: [3.917, 5.664]) and PAF levels (95CI%: [34.511,73.336]) than conventional group (fig. 5).

Comparison of clinical efficacy

At T1, GBE group demonstrated higher total effective than rate conventional group (P<0.05) (table 2).

Table 1: General clinical data

Items	conventional group (n=60)	GBE Group (n=60)	χ^2/t	*P*
Sex[n(%)]			0.307	0.580
Female	24(40.00)	27(45.00)		
Male	36(60.00)	33(55.00)		
Age(years)	69.03±4.38	70.03±4.85	1.186	0.238
Time from onset to admission(h)	11.94±2.89	12.67±2.93	1.362	0.176
BMI(Kg/m^2)	24.51±2.90	25.31±1.87	1.814	0.072
Hypertension [n(%)]				
No	37(61.67)	32(53.33)	0.853	0.356
Yes	23(38.33)	28(46.67)		
Hyperlipemia[n(%)]			0.342	0.559
No	39(65.00)	42(70.00)		
Yes	21(35.00)	18(30.00)		

Table 2: Comparison of clinical efficacy [n(%)]

Group	N	Obvious effect	Effective	Ineffective	Total effective
conventional group	60	1(1.66)	49(81.67)	10(16.67)	50(83.33)
GBE group	60	3(5.00)	55(91.67)	2(3.33)	58(96.67)
χ^2					4.537
P					0.033

Table 3: Comparison of the occurrence of adverse reactions [n(%)]

Group	N	Nausea	Gastrointestinal reactions	Minor rashes	Total
conventional group	60	3(5.00)	2(3.33)	2(3.33)	7(11.67)
GBE group	60	1(1.67)	1(1.67)	1(1.67)	3(5.00)
χ^2					1.745
P					0.186

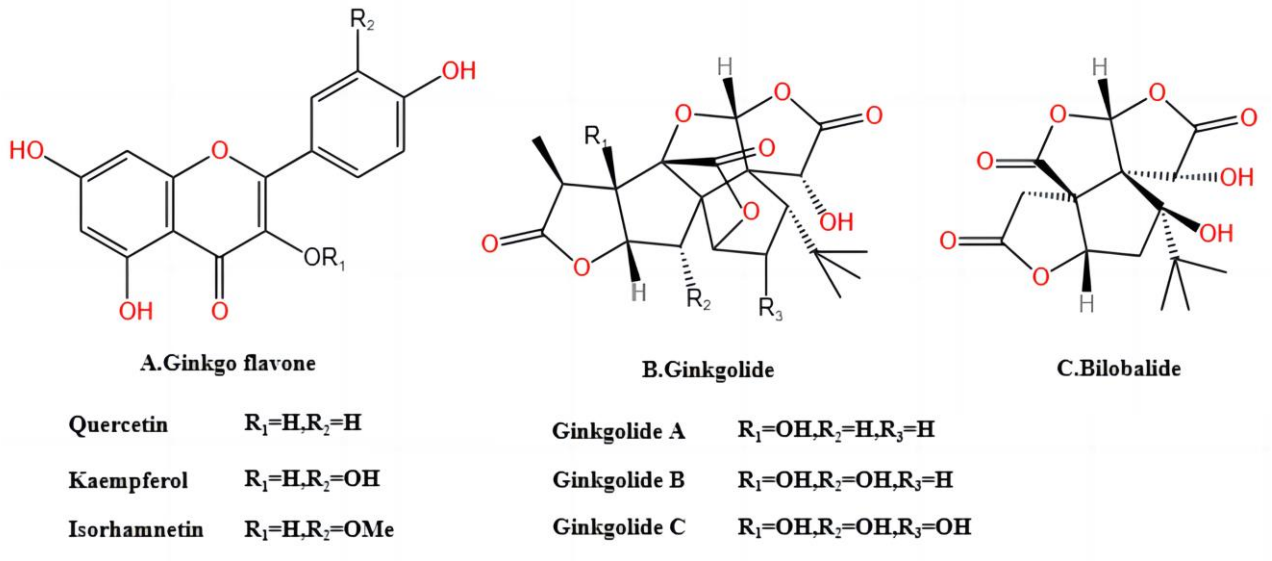
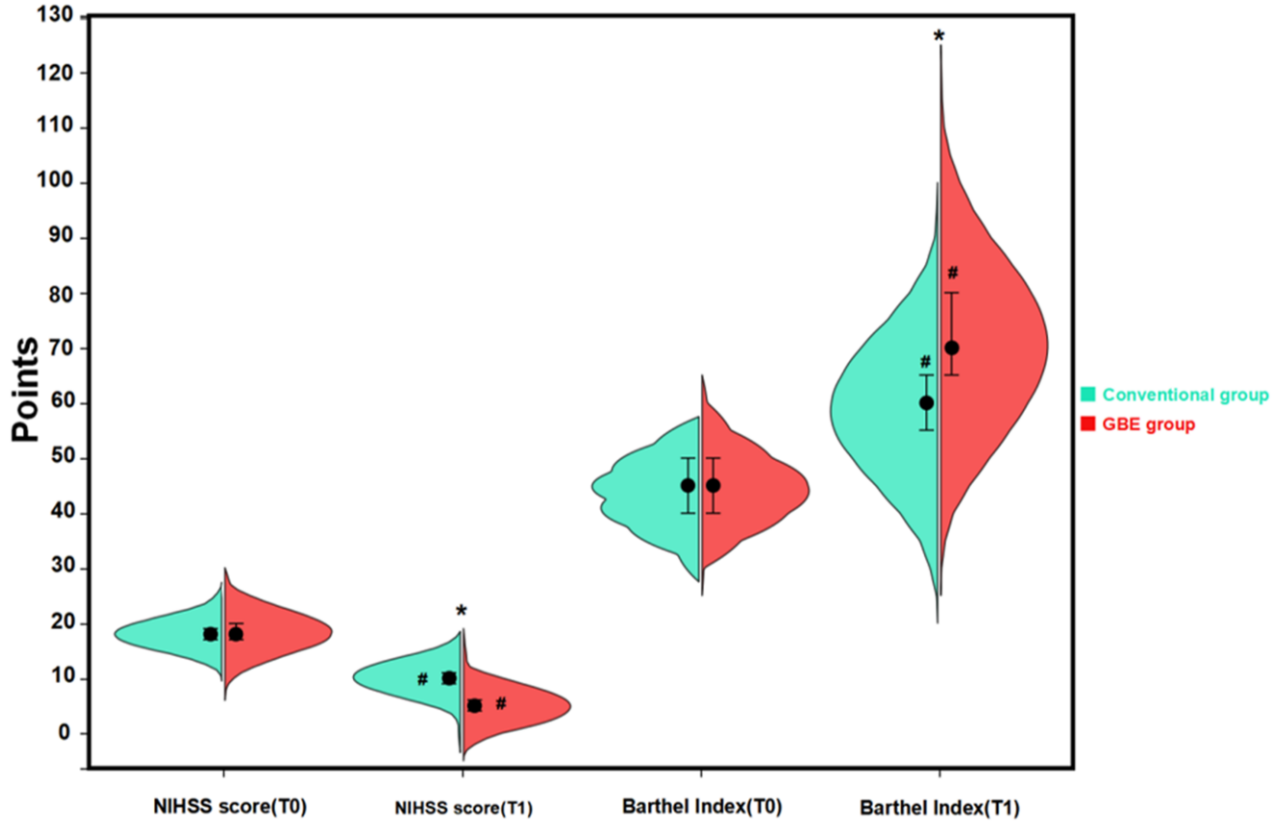
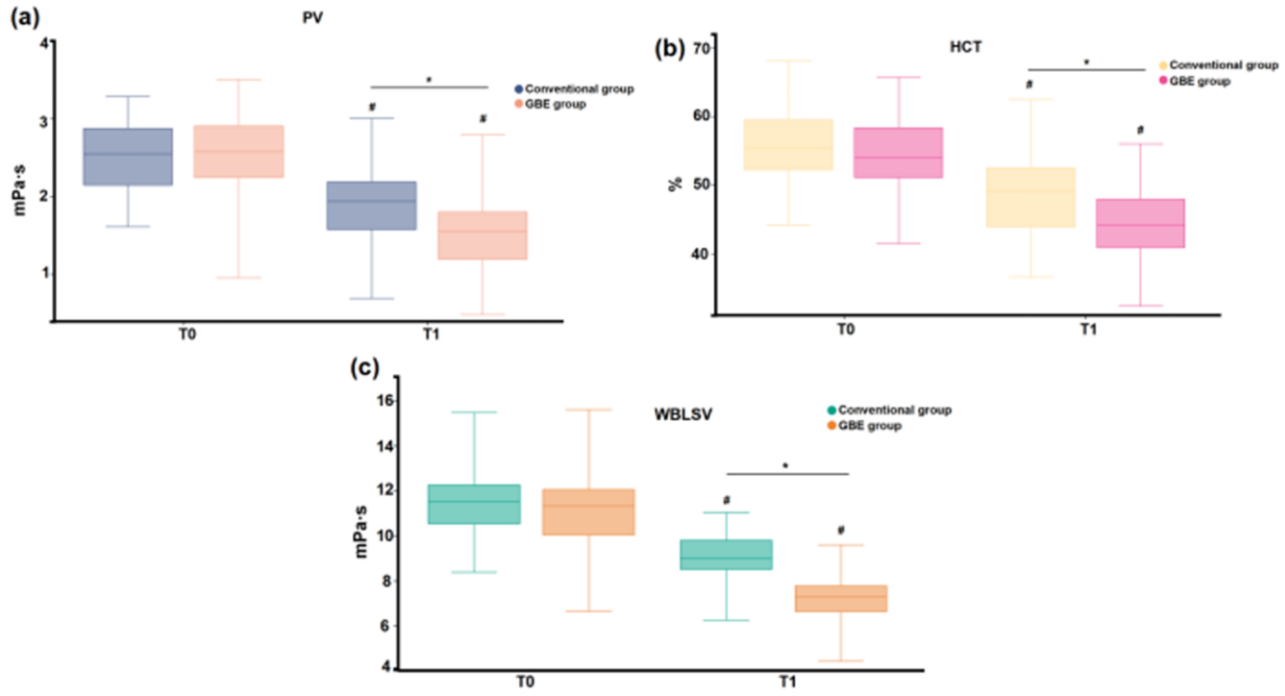


Fig. 2: Chemical structural formulae of some major components in *Ginkgo biloba* extracts. A. Ginkgo flavone; B. Ginkgolide; C. Bilobalide



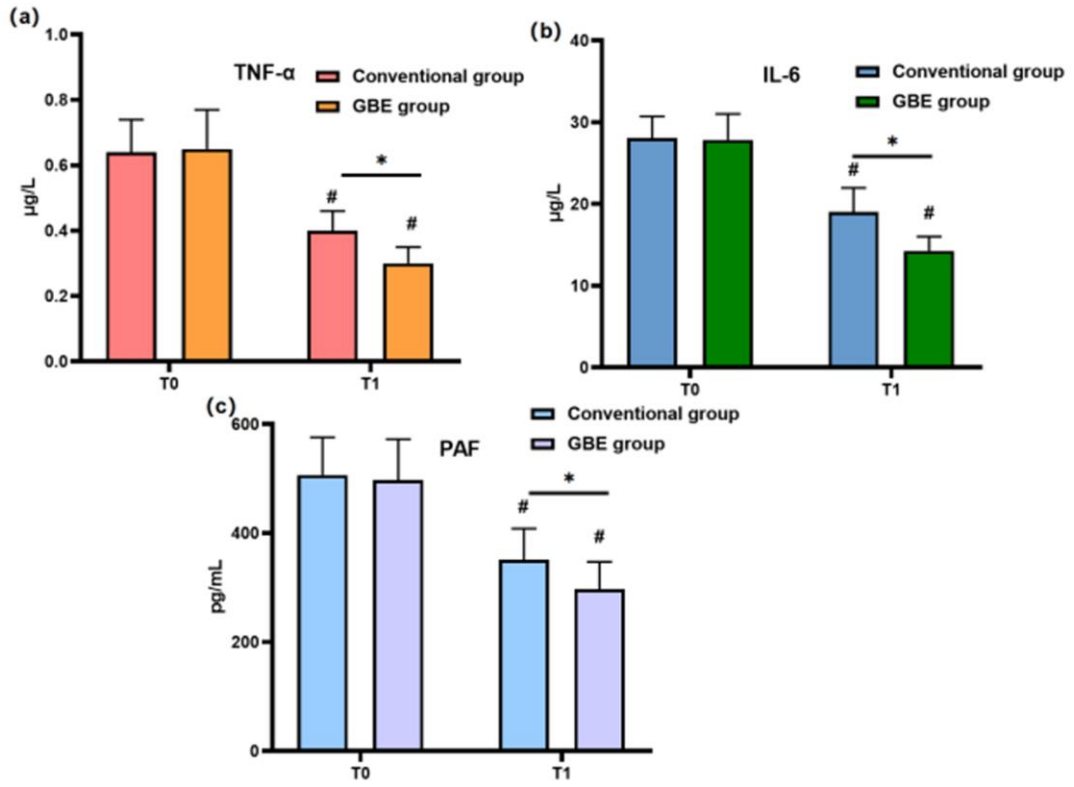
Note:* indicates comparison with conventional group, P < 0.05. # indicates compared with T0, P < 0.05.

Fig. 3: Comparison of neurological function and daily life ability scores



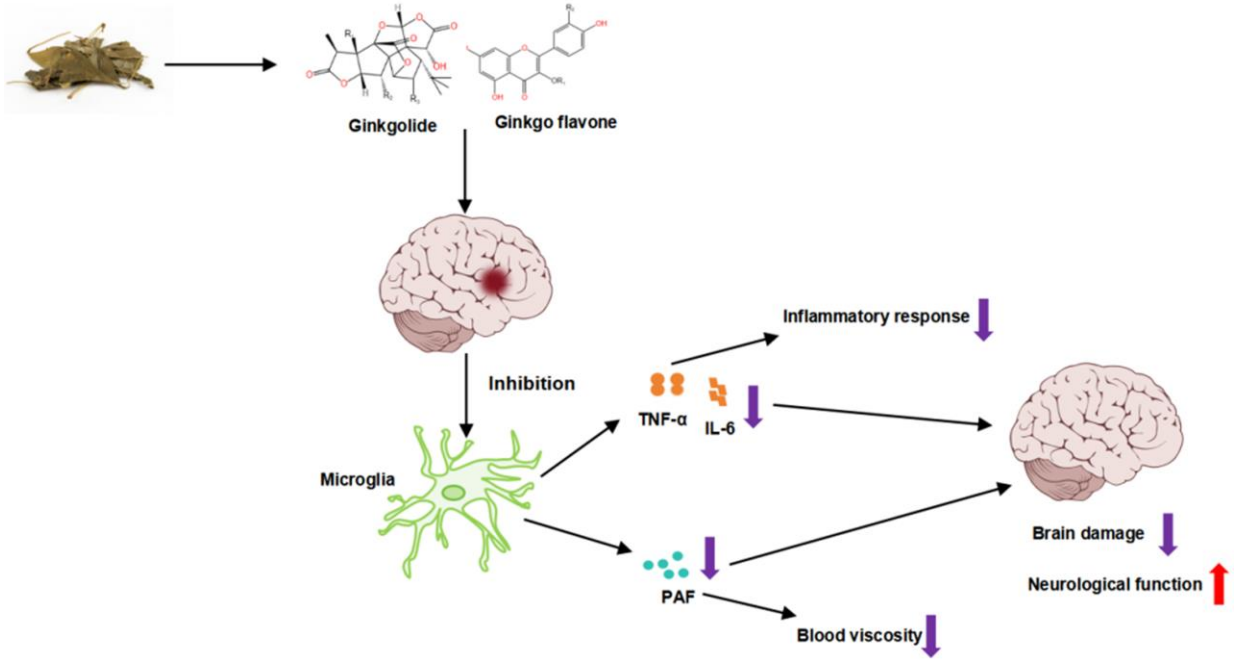
Note:* indicates comparison with conventional group, P < 0.05. # indicates compared with T0 (Before treatment), P < 0.05.

Fig. 4: Comparison of hemorheology indexes. (a) PV: plasma viscosity;(b) Hematocrit: HCT; (c) WBLSV: Whole blood low-shear viscosity



Note:* indicates comparison with conventional group, P < 0.05. # # indicates compared with T0 (Before treatment), P < 0.05.

Fig. 5: Comparison of serum inflammatory factors and PAF levels. (a) TNF-α:Tumor necrosis factor-α; (b) IL-6:Interleukin-6;(c) PAF: Platelet activating factor



Note: As shown in the fig. in this study, GBE reduced blood PAF, TNF-α, and IL-6 levels. Ginkgolide in GBE played a competitive role by acting on target cell membrane receptors, inhibiting the binding of PAF to its receptors, preventing PAF from inducing platelet aggregation and thrombosis, and thereby alleviating cerebral ischemia injury. Ginkgolide and flavonoids effectively inhibit the activation of microglia, down-regulate pro-inflammatory cytokines TNF-α and IL-6 expression, reduce the inflammatory response caused by cerebral ischemia, thus protecting nerve cells and promoting the recovery of nerve function.

Fig. 6: Mechanism of action diagram of *Ginkgo biloba* extract

Comparison of the occurrence of adverse reactions

There was no significant difference in the occurrence of adverse reactions between the two groups during the treatment (P>0.05) (table 3).

DISCUSSION

ICVD is a kind of cerebral blood circulation disorder disease with rapid onset and rapid progress, which is mainly manifested as local cerebral ischemic necrosis caused by cerebral ischemia and hypoxia. In the clinic, the morbidity, mortality and disability rates of elderly ischemic cerebrovascular disease are very high, and accompanied by sensory and neurological dysfunction, and in severe cases, even respiratory and cardiac arrest and other symptoms, which are life-threatening, so timely and effective treatment is very critical (Zhou *et al.*, 2021). In recent years, despite significant advancements in medical technology that have led to an increased survival rate among elderly patients with ICVD, but some of the surviving patients suffer from neurological impairment, which not only reduces the ability of patients' daily life, but also significantly diminishes their overall quality of life, thereby impeding their rehabilitation process (Zuo *et al.*, 2022).

Most Chinese medicine collectively referred to ischemic cerebrovascular disease as stroke disease, that stroke disease is located in the brain, with positive deficiency and accumulation loss as the root, internal wind, fire, blood stasis and phlegm as the standard, a variety of evil and real concomitant, the internal organs of the human body yin and yang imbalance, disorders in the functioning of blood and qi, blood stasis blockage of collaterals, veins and tubes are impassable, unable to reach the brain, triggered by brain orifices obscured and the brain injury and the onset of the blood stasis through the whole of the disease, treatment of qi to invigorate the blood and blood flow to resolve blood stasis method is based on (Zhang *et al.*, 2021). Upon further investigation of TCM, TCM and its active ingredients exhibit noteworthy efficacy in the management of cerebrovascular diseases, which has the characteristics of multi-target and multi-pathway actions. Ginkgo is a plant of Ginkgoaceae and Ginkgo biloba, was first published in Sheng Nong's herbal classic. *Ginkgo biloba* is neutral in nature, sweet, bitter, astringent and flat in flavor and belongs to the heart meridian and the lung meridian and it is a traditional TCM with the functions of invigorating the blood, removing blood stasis and clearing up collaterals. GBE is an effective extract obtained by purification and enrichment from *Ginkgo biloba* and its active ingredients are mostly total flavonoids and ginkgolide terpene lactones, which have significant improvement of cardiovascular system, regulation of blood lipids, antioxidant and anti-inflammatory effects (Ye *et al.*, 2024). Modern medical research has found that GBE is rich in flavonoids and terpene lactones, of which flavonoids have the effects of scavenging oxygen radicals, reducing antioxidant enzyme depletion, inhibiting lipid peroxidation, anti-inflammatory and antithrombotic effects; among terpene lactones, ginkgolide is a potent platelet-activating factor antagonist, which is capable of resisting platelet aggregation, decreasing vascular resistance, improving hemodynamics, inhibiting thrombosis and protecting cerebral tissue after cerebral ischemia and reperfusion (Zhang *et al.*, 2023). GBE, as a TCM preparation, has received widespread attention in the treatment of ICVD in recent years; therefore, this investigation's aim was to explore the medical usefulness and mechanism of GBE in the management of elderly ICVD.

The study outcomes revealed a substantial reduction in NIHSS scores and a notable improvement in the Barthel index for both patient groups after treatment and the NIHSS scores in the GBE group were notably lower and the Barthel index were higher compared to the conventional group. Furthermore, GBE group's overall clinical efficacy was notably superior to that of the conventional group. This indicated that GBE was capable of notably alleviating the clinical symptoms of elderly patients with ICVD, effectively improve the patients' neurological deficits, reduce the neurological damage caused by cerebral ischemia, improve the patients' ability to daily life, and has good clinical efficacy, similar to the results of previous study (Ji *et al*., 2020). The reason may be analyzed because the active components in *Ginkgo biloba* extract, such as ginkgolides and flavonoids, have antioxidant and anti-inflammatory effects, which can protect nerve cells from ischemic and hypoxic damage, thus enhancing the repair ability of the brain nerves, so that the patients' neurological function is restored, and thus the ability of daily life is also improved (Guan *et al.*, 2021). The findings of this study further revealed a significant decrease in the WBLSV, PV and HCT values for both groups after treatment and the GBE group exhibited significantly lower WBLSV, PV and HCT values compared to the conventional group, which is similar to the findings of previous study (Qiu *et al.*, 2020). The observed improvement in these hemorheology indexes suggests that GBE has the capacity to lower blood viscosity and enhance microcirculation, and enhance the protective function of cerebral tissues after ischemia, which can help to alleviate the symptoms of cerebral ischemia; in addition, GBE can diastole blood vessels, promote erythrocyte deformation and local microcirculation, which can improve the patients' hemorheology condition (Xu *et al.*, 2017).

Cytokines are substances that modulate the immune system and play crucial roles in activating, differentiating, and proliferating cells in order to orchestrate the immune response. Certain cytokines including TNF-α and IL-6 possess pro-inflammatory properties and are involved in regulating diverse physiological physiological processes

in brain tissue, including direct effects on the function of endothelial cells, neurons and glial cells. When ICVD occurs, the initial inflammatory response to brain tissue injury is mediated by recruitment through activation of microglia. Glial cells are the brain's resident macrophages, and they are highly activated following brain injury. When ischemia occurs in the brain, activated microglia release pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and other potentially cytotoxic molecules, leading to inflammatory responses and increasing the likelihood of neuronal death, which can lead to cerebral neurological impairment (Zhu *et al.*, 2022, Xu *et al.*, 2022). In addition, there are a large number of PAF receptors in microglia in the brain; PAF is an endogenous phosphoester produced by a variety of cells, including inflammatory cells, vascular endothelial cells, and platelets, and belongs to one of the potent platelet aggregation-inducing activators. Cerebral ischemia and ischemia can activate microglia to produce large amounts of PAF, leading to oxidative stress and inflammatory responses and indirectly inducing neuronal apoptosis; PAF can also cause platelet aggregation, which has a key role in initiating and promoting thrombosis (Yu *et al.*, 2018). It had been shown that reduced blood flow in the central nervous system and neuronal cell damage were linked to elevated concentrations of PAF(Dong *et al.*, 2021). The findings of this study revealed that TNF-α and IL-6 levels were notably lower in GBE group compared to conventional group. This implied that GBE possessed anti-inflammatory properties, capable of suppressing inflammatory responses and mitigating brain tissue damage; additionally, it can inhibit platelet activation and reduce the risk of thrombosis, which helped to treat ICVD. The active ingredients in CBE targeting the treatment of ICVD include total flavonoids and terpene lactones. Among them, ginkgolide, as a natural PAF receptor antagonist, has a molecular mechanism that inhibit PAF from binding to its receptor by acting on the membrane receptor of target cells and exerting a competitive effect, preventing the PAF induced platelet aggregation and thrombosis, lowering blood viscosity, improving blood rheology and thus alleviating the cerebral ischemic injury. In addition, ginkgolides and flavonoid components can effectively inhibit the activation of microglia, down-regulate the expression of pro-inflammatory cytokines TNF-α and IL-6 and attenuate the inflammatory response induced by cerebral ischemia, and thus protect neuronal cells to a certain extent and facilitates the recuperation of neurological function (Dong *et al.*, 2021, Ke *et al.*, 2021, Gachowska *et al.*, 2021)(the mechanism of GBE was illustrated in Fig.6). In this study, there was no statistical difference in the occurrence of adverse reactions between the two groups, indicating that the treatment with GBE did not significantly improve the rate of adverse reactions in patients and it has a certain therapeutic safety (Sha *et al*., 2022).

This study had certain constraints: The sample size collected was small and the sample selection was limited. Our data were collected from elderly patients with ICVD in our hospital and the results may be biased. In the future, the source and number of samples can be expanded and a wider range of patient data can be collected through multi-center cooperation and cross-regional research to further verify the efficacy of GBE. In this study, GBE in the treatment of elderly ICVD duration was 14 days. Although some efficacy could observe in the short term, assessments of long-term efficacy were lacking. In future studies, the duration of treatment can be extended to observe the long-term efficacy of GBE on elderly ICVD and its efficacy and safety can be more comprehensively evaluated through long-term treatment and follow-up. At the same time, there remained a notable absence of comprehensive studies exploring the mechanism of other active ingredients in GBE except total flavonoids and ginkgo terpene lactone in the therapeutic of ICVD in the elderly, and in the future, we can reveal the specific mechanism of the treatment of ICVD through in-depth study of other active ingredients in terms of the target point of action and signaling pathway, in order to establish a more scientific foundation for the clinical use of medication.

CONCLUSION

In summary, GBE has good therapeutic benefits in managing elderly ICVD, effectively facilitate the recuperation of patients' neurological function, has obvious anti-inflammatory effect, improves patients' cerebral circulation and hemorheology indexes, and makes the patients' daily life ability significantly improved, which has a good clinical application value.

REFERENCES

Tang Y and Geng D (2019). Associations of plasma LP (a), Hcy and D-D levels with the subtype of ischemic cerebrovascular disease. *Medicine (Baltimore)*, **98**(11): e14910.

Lin K, Chen L, Wang Y, Xu Y, Wang G, Li H, Pan Y, Ma L and He S (2020). Endovascular treatment of cerebrovascular stenosis with stent for patients with ischemic cerebrovascular disease. *Medicine (Baltimore)*, **99**(47): e23313.

Deguchi I, Osada T, Kohyama S and Takahashi S (2022). Status of neurological deficits after mechanical thrombectomy in elderly patients with ischemia. *J. Clin Neurosci.*, **105**: 16-21.

Zhang H, Jin B, You X, Yi P, Guo H, Niu L, Yin Q, Shi J, Zhang Y and Zhuang P (2023). Pharmacodynamic advantages and characteristics of traditional Chinese medicine in prevention and treatment of ischemic stroke. *Chin. Herb. Med.*, **15**(4): 496-508.

Li XH, Yin FT, Zhou XH, Zhang AH, Sun H, Yan GL and

Wang XJ (2022). The signaling pathways and targets of natural compounds from traditional chinese medicine in treating ischemic stroke. *Molecules*, **27**(10): 3099.

Peng Y, Lin Y, Yu NW, Liao XL and Shi L (2021). The clinical efficacy and possible mechanism of combination treatment of cerebral ischemic stroke with *Ginkgo biloba* extract and low-frequency repetitive transcranial magnetic stimulation. S*ichuan Da Xue Xue Bao Yi Xue Ban*, **52**(5): 883-889.

Zhu T, Wang L, Wang LP and Wan Q (2022). Therapeutic targets of neuroprotection and neurorestoration in ischemic stroke: Applications for natural compounds from medicinal herbs. *Biomed. Pharmacother.*, **148**: 112719.

Yin CY, Lian YP, Xu JD, Liu CM, Cai JL, Zhu L, Wang DJ, Luo LB and Yan XJ (2024). Study on network pharmacology of *Ginkgo biloba* extract against ischaemic stroke mechanism and establishment of UPLC-MS/MS methods for simultaneous determination of 19 main active components. *Phytochem Anal.*, **35**(2): 254-270.

Singh SK, Srivastav S, Castellani RJ, Plascencia-Villa G and Perry G (2019). Neuroprotective and antioxidant effect of *Ginkgo biloba* extract against AD and other neurological disorders. *Neurotherapeutics,* **16**(3): 666-674.

Liu Y, Wu X and Yu Z (2019). Ginkgo leaf extract and dipyridamole injection as adjuvant treatment for acute cerebral infarction: Protocol for systemic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*, **98**(8): e14643.

Pu X, Fu Y, Yang Y and Xu G (2024). *Ginkgo biloba* extract alleviates CCl4-induced acute liver injury by regulating PI3K/AKT signaling pathway. *Heliyon*, **10**(4): e26093.

Kwah LK, Diong J (2014). National Institutes of Health Stroke Scale (NIHSS). *J. Physiother*, **60**(1): 61.

da Costa JC, Manso MC, Gregório S, Leite M and Pinto JM (2022). Barthel's Index: A better predictor for COVID-19 mortality than Comorbidities. *Tuberc. Respir. Dis. (Seoul)*, **85**(4): 349-357.

Zhou J, Shan Y and Hu P (2021). A systematic review and meta-analysis on transcranial Doppler in diagnosing ischemic cerebrovascular disease. *Ann. Palliat. Med.*, **10**(8): 8963-8971.

Zuo L and Sun M (2022). Effects of all-inclusive and hierarchical rehabilitation nursing model combined with acupuncture on limb function and quality of life in elderly patients with cerebral infarction during convalescence. *J. Healthc. Eng*., **2022**: 2654729.

Zhang T, Luo H, Wei D, Xie X, Yang C, Liu B and Gao Y (2021). Traditional Chinese medicine constitution correlated with ischemic stroke: A systematic review and meta-analysis. *Evid. Based Complement. Alternat. Med.*, **2021**: 5524925.

Ye W, Wang J, Little PJ, Zou J, Zheng Z, Lu J, Yin Y, Liu H, Zhang D, Liu P, Xu S, Ye W and Liu Z (2024). Anti-atherosclerotic effects and molecular targets of ginkgolide B from *Ginkgo biloba*. *Acta Pharm. Sin. B*, **14**(1): 1-19.

Zhang L, Fang X, Sun J, Su E, Cao F and Zhao L (2023). Study on synergistic anti-inflammatory effect of typical functional components of extracts of *Ginkgo biloba* leaves. *Molecules*, **28**(3): 1377.

Ji H, Zhou X, Wei W, Wu W and Yao S (2020). Ginkgol Biloba extract as an adjunctive treatment for ischemic stroke: A systematic review and meta-analysis of randomized clinical trials. *Medicine (Baltimore)*, **99**(2): e18568.

Guan YJ, Yang SH, Bai X, Chang WJ and Chen W (2021). Systematic review of efficacy and safety of *Ginkgo biloba* extract 50 in treatment of ischemic stroke. *Zhongguo Zhong Yao Za Zhi*, **46**(22): 5977-5986.

Qiu J, Guo Y, Xu X, Yue H and Yang Y (2020). Ginkgo leaf extract and dipyridamole injection for chronic cor pulmonale: A PRISMA-compliant meta-analysis of randomized controlled trials. *Biosci. Rep.*, **240**(3): BSR20200099.

Xu J, Wang KL, Cao ZY, Cao L, Wang ZZ and Xiao W (2017). Antagonistic effect of ginkgolide homologues on PAF-induced platelet aggregation and neuroprotective effect. *Zhongguo Zhong Yao Za Zhi*, **42**(24): 4716-4721.

Xu M, Wu RX, Li XL, Zeng YS, Liang JY, Fu K, Liang Y and Wang Z (2022). Traditional medicine in China for ischemic stroke: Bioactive components, pharmacology, and mechanisms. *J. Integr Neurosci.*, **21**(1): 26.

Yu WB, Cao L, Zhao YY, Xiao W and Xiao BG (2018). Comparing the role of Ginkgolide B and Ginkgolide K on cultured astrocytes exposed to oxygen-glucose deprivation. *Mol. Med. Rep.*, **18**(5): 4417-4427.

Dong Y, Zhang J, Wang Y, Zhao L, Li R, Wei C, Bai Q, Wan L, Sun L, Feng S, You M, Wang C, Zhang H, He Q, Yu M and Dong Q (2021). Effect of Ginkgolide in Ischemic Stroke patients with large Artery Atherosclerosis: Results from a randomized trial. *CNS Neurosci. Ther.*, **27**(12): 1561-1569.

Ke J, Li MT, Huo YJ, Cheng YQ, Guo SF, Wu Y, Zhang L, Ma J, Liu AJ and Han Y (2021). The synergistic effect of *Ginkgo biloba* extract 50 and aspirin against platelet aggregation. *Drug Des. Devel. Ther.*, **15**: 3543-3560.

Gachowska M, Szlasa W, Saczko J and Kulbacka J (2021). Neuroregulatory role of ginkgolides. *Mol. Biol. Rep.*, **48**(7): 5689-5697.

Sha RN, Tang L, Du YW, Wu SX, Shi HW, Zou HX, Zhang XR, Dong XL and Zhou L (2022). Effectiveness and safety of *Ginkgo biloba* extract (GBE50) in the treatment of dizziness caused by cerebral arteriosclerosis: A multi-center, double-blind, randomized controlled trial. *J. Tradit. Chin. Med.*, **42**(1): 83-89.