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Original Article

Formulation and Evaluation of Nanoemulsion of the Phenolic Content of *Foeniculum vulgare* for Antidepressant and Antihypertensive Potentiality

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ABSTRACT

Objectives: *Foeniculum vulgare* (common name: fennel; family: Umbelifereae) is a well-documented plant with various medicinal properties to manage different types of disease. Depression and hypertension are associated with each other. The study focuses mainly on the evaluation of the antidepressant and antihypertensive effect of the nanoemulsion formulations of the phenolic content of the arial part of *Foeniculum vulgare*. **Materials and Methods:** The nanoemulsion formulation (1% and 2% W/V) formulation was formulated and subjected to *in vivo* screening of its antidepressant activity following forced swim and tail suspension tests in mice, while its antihypertensive effect using salt induces hypertension in wistar rats with BIOPAC power lab. **Results:** The study measured a significant (p<0.01) reduction (p <0.01) by Nanoemulsion of *Foeniculum vulgare* (NFV) in immobility times in mice, which was well comparable to imipramine (15 mg/kg) and so significant (p<0.01) normalization (p <0.01) of increased blood pressure. It was further interpreted significant (p<0.01) increase in the brain level of dopamine and serotonin exhibiting major mechanism behind the antidepressant and antihypertensive potentiality of *Foeniculum vulgare*. **Conclusion:** The study suggested the implementation of the use of NFV in the overall treatment of hypertension associated with depression and vice versa.

Keywords: Nanoemulsion, Essential oil, *Foeniculum vulgare*, Monoamine, Dopamine, Serotonin.

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INTRODUCTION

In the present scenario, depression has become one of the main psychiatric problems in all age groups. In addition, hypertension is gradually becoming a common disorder in any age group due to lifestyle and food habits. Previous scientific studies revealed that depression induces the risk towards uncontrolled hypertension and vice versa.[1] The search for a potent agent with lesser toxicity is ongoing to manage the disorders. In our previous extensive review on *Foeniculum vulgare*, its traditional medicinal importance was revealed without any serious adverse effects.[2] Scientific investigations of *Foeniculum vulgare* revealed its nutraceutical properties along with its bioactive constituents. Researchers observed that different extracts of fennel were found to exhibit a variety of medicinal properties, antimicrobial, cytoprotective, anxiolytic, anticancer, anti-aging, etc. assisting its conventional therapeutic uses.[3-5] The revealed pharmacological properties may be due to the presence of its bioactive components, such as amino acids, phenolic compounds, volatile components, flavonoid aglycons (Acacetin, Kaempferol, Naringenin, Isorhamnetin), oleanolic acid, alpha phellandrene, fenchone, anethole, estragole, methyl chavicol, p-allyl, etc.[6,7] Additionally, the potential of *Foeniculum vulgare* is also investigated for the management of cardiovascular disorders along with antihypertensive[8] and antidepressant[9,10] essential oils of its fruits and seeds, but not reported on arial parts. It has also been evident that the oil from *Foeniculum vulgare* is particularly used in aromatherapy and regarded as a tonic to the nervous.[11] It is evident that hypertension is always associated with depression and vice versa. The aromatherapeutic use of *Foeniculum vulgare oil* is regarded a tonic for the nervous system, which initiated the present investigation to confirm its less proven antidepressant and antihypertensive activity. There are not evident reports about the biological effect of the novel nanoemulsion formulation of this plant for the management of depression as well as hypertension which occurrence is interdependent. For better bioavailability, an attempt has been made to formulate the nanoemulsion of the essential oil of *Foeniculum vulgare* and the aqueous solution has been subjected to evaluation of the antidepressant and antihypertensive potentiality.

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MATERIALS AND METHODS

Collection of plant materials and preparation of extract

The aerial part of the plant was collected from Hapur, Uttar Pradesh. Its well-prepared herbarium was further authenticated from the Taxonomical Department NBPGR, PUSA (New Delhi). The plant was identified as *Foeniculum vulgare*. After authentication, the aerial parts of *Foeniculum vulgare* were collected in bulk from the farms of rural regions near Greater Noida, Uttar Pradesh. The collected plant parts were dried in shade and crushed to powder. Further the powdered plant parts were subjected to hydro-distillation in a Chevenger's apparatus to obtain yellow colored oil (yield: 3.9% W/V). The crude oil of *Foeniculum vulgare* was than dried over anhydrous sodium sulphate to remove the traces of moisture and then stored in cool place in an airtight container.[12] It was also subjected to preliminary phytochemical tests to get idea about the types of chemical constituents present in it.[10,13,14]

Measurement of total phenolic content

Folin-Ciocalteu method was followed to measure the Total Phenolic Content (TPC) of the final extract using UV-vis spectrophotometer as outlined by Meda *et al.*, 2005. It was treated with Folin-Coicalteu reagent and saturated solution of Na_2CO_3.[15] Thirty minutes after the incubation in room temperature, the reaction mixture was diluted to 10 mL with distilled water. The clear solution was subjected to obtain its absorbance at 725 nm. TPC was measured from the standard calibration curve using chlorogenic acid as standard.[13,16]

Nanoemulsion preparation

The self-emulsification process was used to create Nanoemulsion of *Foeniculum vulgare* (NFV) to result a 1% and 2% W/V of the essential oil of *Foeniculum vulgare*. Nonionic surfactants Tween 80 and Span 80 were utilized, together with ethanol. Its nanoemulsion was formulated using olive oil and water as the oil and external phase respectively.[16]

Stability test

The physical stability of NFV was determined by utilizing accelerated storage testing which include centrifugation test, heating cooling test, and freeze-thaw cycle test. It was mainly evaluated for any phase separation and transparency.[17]

Physicochemical characterization of nanoemulsion

Droplet size distribution of the NFV was determined by Particle Size Analyzer (PSA). By using Physica rheometer the viscosity of the optimized NFV was determined.[17]

Experimental animals

In the present investigation the *in vivo* studies were carried out using swiss albino mice (25-30 gm; of either sex) and wistar albino rats (200-300 gm; of either sex), availed from the animal facility of NIET Pharmacy Institute, Greater Noida after approval of the research protocol (IAEC/NIET/20/-1/10) from its Institutional Animals Ethics Committee (CPCSEA Reg No. 1845/Re/S/16/CPCSEA). The animals were maintained in standard temperature and humidity with well access to pallet food and water *ad libitum*. The animals were subjected to a seven-day adaptation period to the laboratory conditions prior to the *in vivo* studies.

In vivo Pharmacologucal Screening of NFV

Gross behavioral study

The research was started with the observation of the behavioral changes in animals due to the oral administration of NFV preparations at the selected doses based on the previous findings. The parameters under consideration were reflexes such as righting, pinna and corneal reflexes along with the motor activity, traction test, muscle tone, stereotyped behavior and awareness to get maximum information about the gross behavioral changes at different time intervals to get appropriate results of the oral NFV administration.[18]

Antidepressant Activity

Tail Suspension Test (TST)

The animals were divided into four different groups (n=6) vid; group-I served as control group and received normal saline; group-II served as the standard group and received imipramine (40 mg/kg; orally); whereas group III and IV served as test groups and received NFV 1% W/V and 2% W/V orally. The animals were observed for the time taken to regain its upright position without motion after hanging at 75 cm height by their tail. The duration of immobility was observed for 6 min at 30, 60 and 90 min after NHV and imipramine treatment.[13]

Forced Swim Test (FST)

The animals were divided into four groups (n=6) in the similar fashion as mentioned for TST study. In fresh water (27°C) filled up to 6 cm of a glass beaker having 11 cm diameter animals were forced to swim for 15 min and considered as a pretesting session. Next day each mouse was forced to swim for 6 min as a basal test session. The study was conducted at 30, 60 and 90 min after NFV administration in the similar manner. On motionless floating of the mouse by keeping its head at water surface and the total length of immobility was noted.[19]

Antihypertensive activity

Antihypertensive activity was carried out by using BIOPAC. Blood pressure of rats diagnosed using BIOPIC with the help

of tail cuff. For this study the rats were divided into five groups (n=6), where group-I served as the control group and treated with saline water; the group-II served as the diseased control induced with hypertension by salt diet and were administered with saline, group-III was treated as standard group and administered with Enalapril (0.5 mg/kg; Intraperitoneally) and group-IV and V were hypertensive rats which received NFV of 1% and 2% W/V (orally) respectively. The rats of group II-V were induced with hypertension by administering high salt diet with 8% salt for six weeks. On completion of salt induction period after the respective groups were administered with enalapril to standard and NFV to test groups IV the rats. The Mean Blood Pressure (MBP), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were noted along with the heart rate by the help of BIOPAC.[20]

Effect of NFV on brain monoamine level

Effect of NFV on brain dopamine level of mice: The NFV treated animals after undergoing FST were subjected to the observation of brain dopamine level. After anaesthetization with high dose of isoflurane the brains of individual animals were dissected and homogenized for 1 min in HCl: butanol solution. Further centrifugation at 3000 rpm was carried out for 10 min and again with hexane and 0.1 M HCl. Afterwards dopamine was assayed in its aqueous phase maintained at 0°C and adding 0.2 mL of the aqueous phase and sodium citrate buffer (pH 6.9) followed by iodine solution for oxidation to which sodium sulphite solution and then acetic acid were added. The recovered sample was subjected to measure the excitation-emission spectra at 330-375 nm using spectrofluorometer. The blank was prepared by reverse adding all the reagents of the oxidation step.[21]

Effect of NFV on brain serotonin level of mice: After distributing the mice in the mentioned groups and stress induction, brain was isolated with all sorts of care as mentioned above in the similar manner. The brain tissue was homogenized with 0.1N HCl at 0°C. After centrifugation, to the clear supernatant 10% zinc sulphate and 1N NaOH were added and then again centrifuged for 20 min. To 1mL of clear supernatant 2N HCl was added. The resultant excitation (nm)/fluorescence (nm) was noted by the help of fluorometer at wavelength 290/550 with the slits of 5/3 and 0.3 as instrument sensitivity.[22]

Analysis of obtained data

The obtained data of the investigation are presented as mean ± Standard Error Mean (SEM) and analysed following one-way Analysis of Variance (ANOVA) by Dunnett's t-test. The results were considered to be significance at p<0.01.

RESULTS

Qualitative estimation of TPC

It is evident from the results of the phytochemical analysis that phytoconstituents present in its extract were mainly alkaloids, flavonoids, tannins, and carbohydrates and water was considered as the ideal solvent for further pharmacological investigations. In the present study the TPC of the extract of *Foeniculum vulgare* was calculated to possess 3.4%.

Physicochemical characterization of NFV

In the present study the formulated NFV was found to remain stable for over 8 months at normal and extreme temperatures without significant particle size changes. In the present investigation, the formulated NFV passed all the tests like stability and characterization test.

Gross behavioral study

NFV was observed to be not any effect on the reflexes of mice. Muscle relaxation and catalepsy in mice were also found to be less effected by NFV administration. On the other hand, NFV was observed to potentiate the stereotyped behavior of mice. All these findings after the overall gross behavior effects of NFV in mice indicated its antidepressant property.

Effect of NFV on TST

TST study on oral administration of NFV (1% and 2% W/V) showed significant (p>0.01) reduction in the immobility period in mice which has been depicted in Table 1. NFV with 1% W/V preparation was observed to possess a decrease in immobility period at different time gap like 30 min (148.9 ± 2.836), 1 hr (145.67 ±3.378) and 90 min (141.3 ± 2.832) in comparison to that of the control group. But in case of 2% W/V NFV exhibited better effect by reducing the immobility period at different time gap like 30 min (141.9 ± 2.369), 1 hr (139.7 ± 2.841) and 90 min (136.7 ± 2.319). The overall reduction of immobility period due to NFV was revealed to be well comparable to imipramine.

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.01 was estimated by Dunnett's test and considered as extremely significant. The results in NFV treated groups are well comparable to that of the standard group.

Effect of NFV on FST

The results measured in FSV model revealed that NFV reduced the immobility period of mice significantly (p<0.01) and the results of this study are viewed in Table 2. At 1% W/V NFV exhibited effective decrease in immobility period NFV at its 1% W/V dose found to exhibit reduced immobility period of mice at a time gap of 30 min (145.67± 2.841), 1 hr (139.78 ± 2.412) and 90 min (119.43 ± 1.231) in comparison to that of the control group. It manifested better results at its higher dose (2% W/V) in a similar time interval (138.51 ± 2.129, 122.45± 1.619 and 113.51 ± 2.145 respectively) and observed to be better compared to imipramine.

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation

Table 1: Antidepressant activity of NFV following TST model.

Name of group	Treatment	Increased immobility time (sec.)		
		30 min.	60 min.	90 min.
Control	Normal saline	243.2 ± 1.302	246.3 ± 1.256	249.5 ± 0.922
Standard	Imipramine (40 mg/kg)	139.8 ± 2.342*	133.8 ± 2.517*	126.7 ± 3.254*
Test - I	NFV (1% W/V)	148.9 ± 2.836	145.67±3.378	141.3 ± 2.832*
Test - II	NFV (2% W/V)	141.9 ± 2.369	139.7 ± 2.841*	136.7 ± 2.319*

Table 2: Antidepressant activity of NFV by forced swim test (FST).

Name of group	Treatment	Increased immobility time (sec.)		
		30 min.	60 min.	90 min.
Control	Normal saline	243.2 ± 1.302	246.3 ± 1.256	249.5 ± 0.922
Standard	Imipramine (40 mg/kg)	121.43 ± 2.659*	112.3 ± 3.128*	109.8 ± 2.267*
Test - I	NFV (1% W/V)	145.67± 2.841	139.78 ± 2.412	119.43 ± 1.231*
Test - II	NFV (2% W/V)	138.51 ± 2.129	122.45± 1.619*	113.51 ± 2.145*

against control *p<0.01 was estimated by Dunnett's test and considered as extremely significant. The results in NFV treated groups are well comparable to that of the standard group.

Antihypertensive effect of NFV

In diseased control group the treatment of six weeks salt diet exhibited significant (p<0.05) rise in all the parameters like MBP, SBP and DBP on comparison with the control group. The antihypertensive effect of NFV at its both the doses (1% and 2% W/V) was revealed on observing their significant (p<0.01) decrease in MBP, SBP and DBP in hypertensive rats (Table 3). It has also been exhibited that the heart rate of the animals with salt diet was significantly (p<0.01) normalized by NFV treatment (Table 3). When the results were interpreted it was observed that NFV was having well comparable antihypertensive potentiality to that of the standard drug enalapril.

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.01 was estimated by Dunnett's test and considered as extremely significant. The results in NFV treated groups are well comparable to that of the standard group. MBP: Mean Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic blood pressure.

Effect of NFV on brain dopamine level of mice

In the brain dopamine level test, it was observed that in control group the animals were found to have decreased brain dopamine level of 5.67±0.33 which was lower was less than the normal brain dopamine level of mice (24 µg/gm of brain tissue). On the other hand, the brain tissue of the NFV treated mice showed increased dopamine level to that of the control group and brought it to the normal level. NFV at 2% W/V showed significant (p<0.01) rise in the brain dopamine level (22.67±0.62) on comparison to that of the control group and found to normalize it. NFV at 1% W/V also exhibited rise in the brain dopamine level to 21.83±0.543 which was a lesser extent reflecting the dose dependent induction of brain dopamine level. was also observed to increase the dopamine level but in lesser extent. It is evident that increase in dopamine level is a major pathway for antidepressants as in case of imipramine (25.83± 0.43) in this study.[21] The observation of rise in brain dopamine level by NFV indicated the relief of depression in mice (Figure 1).

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.01 was estimated by Dunnett's test and considered as extremely significant. The results of Test 1 and Test 2 represents that of NFV 1% *WN* and 2% W/V treated groups respectively which are well comparable to that of the standard group.

Effect of NFV on brain serotonin level of mice

After FST model it was observed that the brain serotonin level was reduced to 84.83 ± 0.83 in the control group animals which is lower than the normal brain concentration of serotonin (84.5±2.13 µg/gm of brain tissue). NFV at 2%W/V exhibited potentiation of brain serotonin level to 106.17 ± 1.759 significantly (p<0.01) in comparison to the control group mice. Whereas, at 1% W/V it exhibited lesser level of increase in brain concentration of serotonin (110.67±0.31). The elevation of brain concentration of serotonin level is the prime mechanism behind the antidepressant activity of most agents like imipramine (110.67 ± 1.33).[23] The well comparable rise in brain serotonin concentration by the administration of NFV to imipramine may be the mechanism behind its antidepressant potentiality (Figure 2).

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.01 was estimated by Dunnett's test and considered as extremely significant. The results of Test 1 and Test

Table 3: Antihypertensive activity of NFV in rats.

Name of group	Treatment	MBP (mmHg)	SBP (mmHg)	DBP (mmHg)	Heart rate (beats/min)
Control	Normal saline	112.45±2.25	124.27±1.87	84.97±1.67	319.67±2.99
Diseased control	Salt diet	148.29±3.12^{a*}	158.57±2.17 ^{a*}	111.67±1.93 ^{a*}	351.23±3.19 ^{a*}
Standard	Enalapril (0.5 mg/kg) + Salt diet	105.11±1.34^{b*}	123.12±2.07^{b*}	79.09±1.67 ^{b*}	314.45±2.89^{b*}
Test - I	NFV (1% W/V) + Salt diet	121.54±1.99^{b*}	136.23±2.31^{b*}	86.45±1.57 ^{b*}	321.34±3.19^{b*}
Test - II	NFV (2% W/V) + Salt diet	110.13±2.61^{b*}	127.56±1.19^{b*}	83.67±1.98^{b*}	318.61±3.22^{b*}

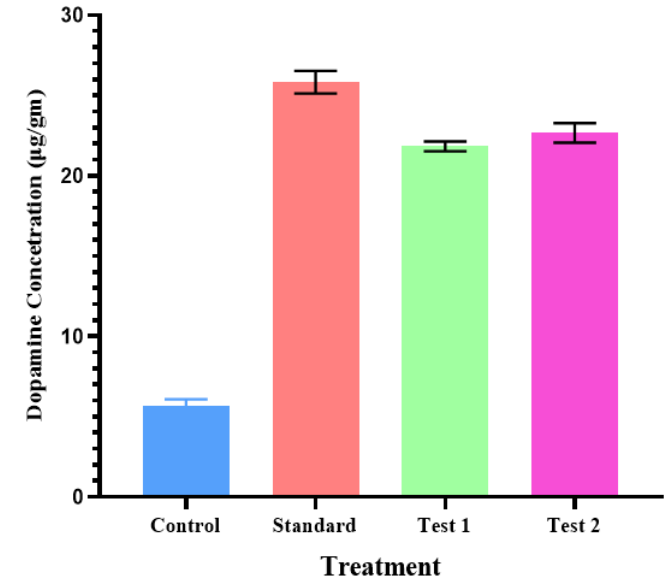

Figure 1: Estimation of the effect of NFV on the dopamine concentration in brain.

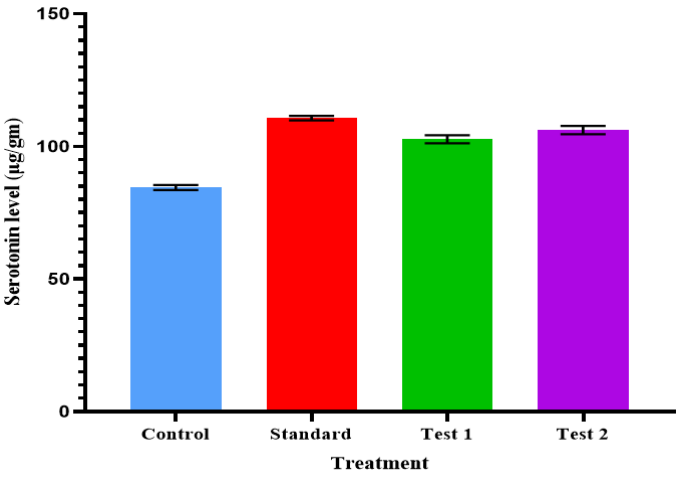

Figure 2: Estimation of the effect of NFV on the serotonin concentration in brain of mice.

2 represents that of NFV 1% *WN* and 2% W/V treated groups respectively which are well comparable to that of the standard group.

DISCUSSION

In the present research, the *Foeniculum vulgare* was illustrated to possess antidepressant activity which was also reflected from the gross behavioural study in mice. The etiologic of depression has involved the biogenic pathway and suggests the disease is associated with the deficiency of monoamines like serotonin, dopamine and norepinephrine in central nervous system and all conventional antidepressants enhance the effects of the monoamine neurotransmitters.[24] Furthermore, it was confirmed to exhibit potent antihypertensive effect which was well comparable to the marketed drug enalapril. It is evident that antidepressant agents give rise to enhanced dopamine and serotonin concentration in brain and NFV exhibited significant rise in brain concentration of both of these mnoamines. On the other hand, depression may also be a risk to start hypertension[25] and literature shows that the reduced dopamine level at important sites of brain is a condition of induction of hypertension.[24] Previous scientific studies reflect the impact of serotonin on the regulation of blood pressure mainly by reducing the cardiac output which supports the present investigation of antihypertensive effect of NFV is also associated with the observed enhanced brain serotonin level.[26] This indicates the major mechanism behind its antidepressant property is by enhancing the brain concentration of dopamine and serotonin. Previous findings also observed the antioxidant potentiality of *Foeniculum vulgare* which may be a supportive protective reason supporting its antidepressant and antihypertensive potentiality.[14,27] All these previous scientific findings support the effective mechanism behind the antidepressant and antihypertensive properties of NFV as its ability to raise the brain dopamine and serotonin level.

CONCLUSION

The overall study reflects the novel the novel approach of the research for formulating the better bioavailable nanoemulsion of the essential oil of the areal parts of *Foeniculum vulgare* and exploring its less revealed biological activities which may be helpful in further studies of the NFV in human population in a systematic manner. The observed dose dependent antidepressant and antihypertensive properties of NFV which were no doubt well comparable imipramine and piracetam respectively. The antidepressant and antihypertensive activities of NFV was observed to be dependent with quick onset and sustained prolong effect which might be due to its nanoemulsion formulation. As depression is a common feature in hypertensive patients and hypertension is a risk to depression, the study suggests the therapeutic implication of *Foeniculum vulgare* as a cost effective and potent management of depression associated with hypertension and vice versa.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SEM: Standard error mean; **gm:** Gram; **mL:** Mili liter; **mg:** Milligrams; **Kg:** Kilograms; **NFV:** Nanoemulsion of *Foeniculum vulgare*; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **NaOH:** Sodium hydroxide; **HCl:** Hydrochloric acid; **FST:** Forced Swim Test; **TST:** Tail Suspension Test; **W/V:** Weight per volume; **TPC:** Total Phenolic Content; **MBP:** Mean blood pressure, **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **ANOVA:** Analyzed of variance.

SUMMARY

Foeniculum vulgare (Family: Umbelliferae) is a reachable source of medication in every Indian kitchen. In the present study an effort has been made to explore its novel nanoemulsion formulation for unrevealed antidepressant and antihypertensive potentiality. The target of the present research was based on the previous evidence of phenolic compounds are having efficacy against depression and hypertensive. To achieve a fruitful result the nanoemulsions of the are formulated from the phenolic content of its arial parts. Further successive *in vivo* models were adopted to screen its medicinal importance for the overall management of depression and hypertension. Fortunately, the NAV exhibited significant dose dependent antidepressant and antihypertensive activity with quick onset and sustained prolong effect. The present study concluded the potential effect of NAV in the overall management of depression and hypertension.

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