

Anticandidal efficiency of *Cinnamomum zeylanicum* extracts against vulvovaginal candidiasis

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The high incidence of *Candidal* vulvovaginitis (CVV) among pregnant women and its treatment during pregnancy is a challenge as the antifungal therapy is associated with foetal abnormalities. Additionally, various *Candida* species exhibit resistance to commonly used antifungal agents. Hence, there is a need to develop new therapeutic strategies against CVV. In the present study, we have evaluated the antifungal activity of cinnamon extracted by four solvents with different degrees of polarity against common *Candida* pathogens. The ethyl acetate extract of cinnamon was the most effective solvent extract and exhibited the highest antifungal activity against *Candida albicans*, *Candida tropicalis* and *Candida glabrata*, with an inhibition zone diameter of 32.47, 32.1 and 16.7 mm respectively. GC-MS revealed that cinnamon ethyl acetate extract comprised of 1-phenylpropene-3,3-diol diacetate (68.5%), eugenol (11.6%), cinnamic acid (8.2%), cinnamaldehyde (6.1%) and 6-ethyl-3,4-dimethylphenol (5.4%). Minimum inhibitory concentration of cinnamon ethyl acetate extract against *C. albicans* and *C. tropicalis* was 0.5 mg/disc, while that against *C. glabrata* was 1 mg/disc. Minimum fungicidal concentration of cinnamon ethyl acetate extract against *C. tropicalis* was 1 mg/disc, while that against *C. albicans* and *C. glabrata* was 2 mg/disc respectively.

Keywords: Antifungal activity, *Candida*, *Cinnamomum zeylanicum*, pregnant women, vulvovaginitis.

GLOBALLY, about 75% women suffer from episodes of vulvovaginal candidiasis (VVC) during their lifetime, and about 5–10% of women have recurrent episodes of VVC¹. *Candida* vaginitis is characterized by vaginal burning sensation, pruritus, irritation, odour and vaginal discharge². Epidemiological studies have revealed that *Candida albicans* is the primary etiological agent for vaginitis, followed by other non-*albicans* species such as *Candida glabrata* and *Candida tropicalis*^{3–5}. The pathogenesis of VVC is associated with several fungal virulence factors such as adhesion, biofilm formation, production of extracellular enzymes and hyphae formation^{6–11}. VVC is also associated with several host factors such as excessive use of antibiotics, pregnancy, immuno-

suppression and diabetes mellitus^{12–15}. Other factors such as the use of oral contraceptive pills, intrauterine devices, and poor sexual hygiene have also been reported to be associated with increased risk for developing VVC^{16–18}. According to recent studies, pregnant women are more susceptible to VVC^{13,19,20}. The high infection rate among pregnant women may be due to the enhanced secretion of sex hormones during pregnancy, especially during the last trimester, where the sex hormones are present at maximum level^{13,21}. The enhanced level of progesterone and estrogen has been reported to increase the amount of glycogen in the vaginal epithelium, which is ideal for the growth of *Candida*^{22,23}. Prescription of antifungal drugs during pregnancy presents a challenge as they are associated with teratogenicity and foetal toxicity²⁴. Recently, several *Candida* strains, especially *C. glabrata*, were reported to exhibit resistance to antifungal drugs^{25,26}. The emergence of multidrug resistant candidal strains in addition to high infection rate with *Candida* vaginitis among pregnant women necessitates the formulation of new and safe antifungal drugs. So the objective of this study was to evaluate the antifungal activity of *Cinnamomum zeylanicum* extracts against different *Candida* pathogens as a potential and safe alternative therapy to the conventional antifungal drugs for treatment of VVC in pregnant women.

C. zeylanicum barks were collected from the local market in Saudi Arabia. They were washed using distilled water, disinfected, and allowed to dry. The dried plant material was ground using a mechanical mortar to pass through a 100 mm sieve. The phytochemicals in the plant material were extracted using four solvents with different degrees of polarity in order to ensure complete extraction of all active ingredients possessing antimicrobial activity. The dried plant material was extracted using different solvents based on their degree of polarity: methanol > ethyl acetate > di-ethyl ether > *n*-hexane with polarity index of 5.1, 4.4, 2.8 and 0.1 respectively. The plant powder (50 g) was added to 200 ml of solvent and extraction was allowed to continue over a magnetic stirrer for 48 h. The extracted solution was filtered and centrifuged at 6000 rpm for 10 min to remove the plant residues. Finally, the extracts were concentrated using a rotatory evaporator, sterilized using Millipore filter and stored at 4°C. The extract yield was calculated according to the formula

$$\text{Percentage extract yield} = (R/S) \times 100,$$

where *R* is the weight of extract residues sample and *S* is the weight of plant raw sample.

Three identified *Candida* strains, viz. *C. albicans*, *C. tropicalis* and *C. glabrata* were used in the study. All the pathogenic strains were obtained from the culture collection of King Khaled Hospital, Riyadh, Saudi Arabia. *Candida* isolates were subcultured onto Sabouraud

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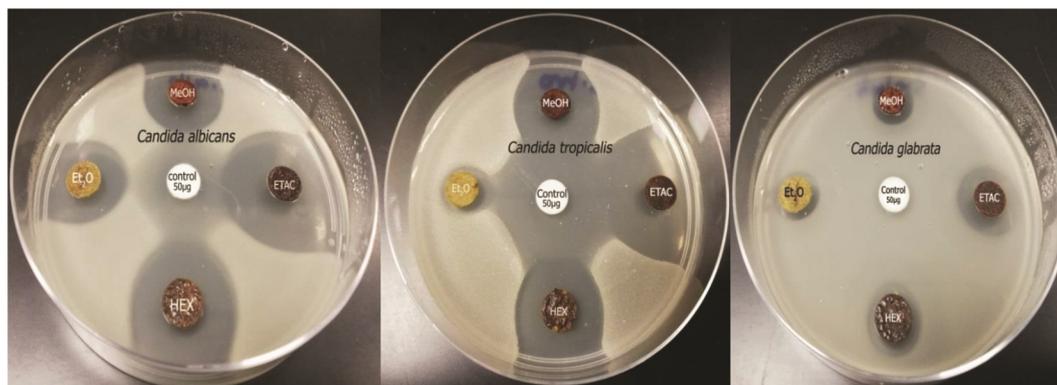


Figure 1. Assay for evaluating the antifungal activity of *Cinnamomum zeylanicum* extracts (10 mg) against *Candida* vaginitis pathogens. MeOH, Methanolic extract; ETAC, Ethyl acetate extract; HEX, *n*-Hexane extract; Et₂O, Diethyl ether extract; Control, Terbinafine antifungal drug (50 µg/disc).

dextrose agar medium (SDA) and incubated at 35°C for 48 h to attain fresh inoculum.

Candida strains were subcultured onto SDA slants for 48 h at 35°C. The candidal growth was harvested using 5 ml of sterile saline solution. The viable cell count for each *Candida* strain was adjusted to 10⁷ CFU/ml by adjusting the absorbance (30%) at 530 nm using a spectrophotometer.

The susceptibility of *Candida* strains to different extracts of *C. zeylanicum* was evaluated using the disc diffusion method. For this, 10 ml of SDA medium was poured into sterile petri dishes as a basal layer followed by 15 ml of seeded medium which was previously inoculated with 1 ml of *Candida* suspension per 100 ml of medium to attain a final concentration of 10⁵ CFU/ml. Sterile filter paper discs (8 mm in diameter) were loaded with 10 mg of different *C. zeylanicum* extracts and placed over SDA plates. A paper disc loaded with 50 µg/disc of terbinafine (Novartis, Switzerland) was used as positive control. The plates were incubated for 2 h in the refrigerator to allow diffusion of plant extracts throughout the medium. The plates were then incubated at 35°C for 48 h and inhibition zone diameters were recorded using a Vernier caliper as an indication of antifungal potency.

The inhibitory concentration of *C. zeylanicum* ethyl acetate extract was evaluated using the disc diffusion method. Sterile filter paper discs were loaded with different concentrations of *C. zeylanicum* ethyl acetate extract. The discs were placed over seeded plates of microbial suspension previously prepared of concentration 10⁵ CFU/ml of medium. The plates were incubated in the refrigerator at 5°C for 2 h to allow diffusion of extract throughout the medium. The plates were then incubated at 35°C for 24 h and the diameter of the inhibition zones corresponding to different extract concentrations was recorded.

The minimum fungicidal concentration (MFC) was evaluated to determine the lowest concentration of *C. zeylanicum* extract exhibiting fungicidal activity. Inocula were taken from inhibition zones of minimum inhibitory

concentration (MIC) plates and streaked onto freshly prepared SDA plates. The plates were incubated at 35°C for 48 h and the lowest concentration that exhibited no fungal growth was considered to be MFC.

Phytochemical analysis of different plant extracts exhibiting antifungal activity was performed by GC-MS using head space method (GCMS-QP2010 Plus, Shimadzu, Japan). The extracts were analysed using VF-5MS capillary column (30 m × 0.25 mm; 0.25 µm film thickness). Conditions of operation were as follows: injection and detector temperature were 250°C and 300°C respectively; helium as a carrier gas with flow rate of 1.0 ml/min; split ratio of 1 : 50. The oven was programmed at 50°–300°C with a ramp rate of 7°C/min. The conditions for mass spectrometry were as follows: mass range *m/z* from 40 to 400 amu; ionization potential of 70 eV; electron multiplier energy of 2000 V. The active chemical compounds in different cinnamon extracts were identified by comparing with the spectral mass data and relative retention time in the NIST database.

Antifungal activity data of different *C. zeylanicum* extracts against common *Candida* pathogens were evaluated through one-way analysis of variance and Tukey's multiple-comparison test using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA, USA). The difference was considered statistically significant when the *P*-value was less than 0.05.

The yield of cinnamon extract varied with the solvent used, as the highest yield productivity was obtained using methanol solvent (12.16%) while the yield using ethyl acetate, *n*-hexane and diethyl ether solvents was 0.21%, 0.74% and 1.17% respectively. The difference in extraction yield can be attributed to the differential polarity of the solvents used.

All *C. zeylanicum* extracts showed antimicrobial activity against different *Candida* strains (Figure 1). The ethyl acetate extract of *C. zeylanicum* showed highest antifungal activity against *C. albicans*, *C. glabrata* and *C. tropicalis* with inhibition zone diameter of 32.47, 16.7 and

Table 1. Screening of the most effective *Cinnamomum zeylanicum* extracts against *Candida* species

<i>C. zeylanicum</i> extracts (10 mg/disc)	Inhibition zone diameter (mm) of <i>Candida</i> pathogens		
	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>
Diethyl-ether	23.07 ± 0.16	12.50 ± 0.12	10.93 ± 0.15
Ethyl acetate	32.47 ± 0.20	32.10 ± 0.17	16.70 ± 0.12
Methanolic	24.07 ± 0.09	24.50 ± 0.12	12.17 ± 0.15
<i>N</i> -Hexane	20.93 ± 0.09	22.90 ± 0.17	11.67 ± 0.09
Control (50 µg/disc)	26.20 ± 0.06	28.87 ± 0.37	9.60 ± 0.06

Table 2. Determination of minimum inhibitory concentration of ethyl acetate extract of *C. zeylanicum* against *C. albicans* and *C. tropicalis*

Concentration of <i>C. zeylanicum</i> extract (mg/disc)	Inhibition zone diameter (mm) of <i>Candida</i> pathogens	
	<i>C. albicans</i>	<i>C. tropicalis</i>
0.125	0.00 ± 0.00	0.00 ± 0.00
0.250	0.00 ± 0.00	0.00 ± 0.00
0.500	10.47 ± 0.15	9.07 ± 0.09
1.000	22.57 ± 0.50	14.07 ± 0.49
2.000	26.20 ± 0.35	19.60 ± 0.46
4.000	28.40 ± 0.69	21.87 ± 0.26

Table 3. Determination of minimum inhibitory concentration of ethyl acetate extract of *C. zeylanicum* against *C. glabrata*

Concentration of <i>C. zeylanicum</i> extract (mg/disc)	Inhibition zone diameter (mm) of <i>C. glabrata</i>
0.50	0.00 ± 0.00
1.00	8.60 ± 0.25
2.00	11.67 ± 0.12
4.00	13.13 ± 0.15
8.00	13.93 ± 0.23
10.0	14.85 ± 0.06

Table 4. Phytochemical analysis of *C. zeylanicum* *n*-hexane extract

Compounds	Chemical formula	Molecular weight	Retention time (min)	Percentage of total
Cuminaldehyde	C ₁₀ H ₁₂ O	148	6.309	5.71
1-Phenylpropene-3,3-diol diacetate	C ₁₃ H ₁₄ O ₄	234	7.201	7.80
Isoeugenol	C ₁₀ H ₁₂ O ₂	164	8.964	14.21
Isolodene	C ₁₅ H ₂₄	204	9.510	3.99
Isocaryophyllene	C ₁₅ H ₂₄	204	10.524	13.99
γ-Muuroolene	C ₁₅ H ₂₄	204	11.834	8.26
Curcumene	C ₁₅ H ₂₂	202	11.925	8.13
D-Germacrene	C ₁₅ H ₂₄	204	12.256	4.84
α-Muuroolene	C ₁₅ H ₂₄	204	12.458	2.33
δ-Cadinene	C ₁₅ H ₂₄	204	13.090	4.48
α-Calacorene	C ₁₅ H ₂₀	200	13.581	4.94
γ-Himachalene	C ₁₅ H ₂₄	204	15.810	7.59
T-Muurolol	C ₁₅ H ₂₆ O	222	16.176	8.81
α-Muurolol	C ₁₅ H ₂₆ O	222	16.268	4.90

32.1 respectively (Table 1). The non-albicans *Candida* species, *C. glabrata* and *C. tropicalis*, exhibited low susceptibility to diethyl ether extract of *C. zeylanicum* with

inhibition zone diameter of 10.93 and 12.50 respectively. The anticandidal activity of all *C. zeylanicum* extracts against *C. albicans*, *C. glabrata* and *C. tropicalis* was significantly different ($P < 0.05$) than that of the positive control (terbinafine). There was no significant difference in anticandidal activity between the methanol and *n*-hexane extracts of *C. zeylanicum* against *C. glabrata* ($P > 0.05$).

The lowest concentration of plant extracts exhibiting antimicrobial activity is defined as the MIC. *C. zeylanicum* ethyl acetate extract is an highly effective anticandidal extract; hence its MIC was evaluated against different *Candida* strains. The MIC of *C. zeylanicum* ethyl acetate extract against *C. albicans* and *C. tropicalis* was 0.5 mg/disc (Table 2), while a higher concentration was recorded against *Candida glabrata* (1 mg/disc) (Table 3). *C. zeylanicum* ethyl acetate extract was highly effective against *C. albicans* with MIC of 0.5 mg/disc, which was lower than that obtained in an earlier study of cinnamon oil against *C. albicans* strains (1 mg/ml)²⁷.

MFC is defined as the lowest concentration of the extract that exhibits fungicidal activity. MFC of *C. zeylanicum* ethyl acetate extract for *C. tropicalis* was 1 mg/disc as no growth was detected, while it was 2 mg/disc for *C. albicans* and *C. glabrata* respectively. The above results of MIC and MFC indicate that *C. tropicalis* is more sensitive to *C. zeylanicum* extract compared with *C. albicans* and *C. glabrata*.

GC-MS analysis of *C. zeylanicum* *n*-hexane extract included isoeugenol (14.21%), isocaryophyllene (13.99%), *t*-muurolol (8.81%), γ-muuroolene (8.26%), curcumene (8.13%), 1-phenylpropene-3,3-diol diacetate (7.8%), γ-himachalene (7.59%), cuminaldehyde (5.71%),

Table 5. Phytochemical analysis of *C. zeylanicum* methanolic extract

Compounds	Chemical formula	Molecular weight	Retention time (min)	Percentage of total
1-Phenylpropene-3.3-diol diacetate	C ₁₃ H ₁₄ O ₄	234	7.390	14.34
1H-Indazole, 3 methyl	C ₈ H ₈ N ₂	132	7.550	12.52
5-Methylamino-1,3,4-thiadiazole-2-one	C ₃ H ₅ N ₃ OS	131	7.654	18.29
α -Copaene	C ₁₅ H ₂₄	204	9.526	2.59
4-Propylbenzoyl chloride	C ₁₀ H ₁₁ ClO	182	10.100	4.23
Cinnamic acid	C ₉ H ₈ O ₃	164	11.147	22.71
α -Muurolol	C ₁₅ H ₂₄	204	12.460	16.11
δ -Cadinene	C ₁₅ H ₂₄	204	13.083	2.52
1 Methyl 2-benzyl-3-methoxy-3-thioxopropanoate	C ₁₂ H ₁₄ O ₃ S	238	13.528	6.14

Table 6. Phytochemical analysis of *C. zeylanicum* ethyl acetate extract

Compounds	Chemical formula	Molecular weight	Retention time (min)	Percentage of total
1-Phenylpropene-3.3-diol diacetate	C ₁₃ H ₁₄ O ₄	234	7.461	68.56
6-Ethyl-3,4-dimethylphenol	C ₁₀ H ₁₄ O	150	7.800	5.45
Eugenol	C ₁₀ H ₁₂ O ₂	164	9.061	11.67
Cinnamic acid	C ₉ H ₈ O ₃	164	10.985	8.22
<i>o</i> -Methoxy cinnamaldehyde	C ₁₀ H ₁₀ O ₂	162	13.381	6.10

Table 7. Phytochemical analysis of *C. zeylanicum* diethyl ether extract

Compounds	Chemical formula	Molecular weight	Retention time (min)	Percentage of total
1-Phenylpropene-3.3-diol diacetate	C ₁₃ H ₁₄ O ₄	234	7.91	10.99
Eugenol	C ₁₀ H ₁₂ O ₂	164	9.183	23.98
α -Copaene	C ₁₅ H ₂₄	204	12.512	2.85
α -Muurolene	C ₁₅ H ₂₄	204	13.153	24.22
δ -Cadinene	C ₁₅ H ₂₄	204	13.153	30.97
1 Methyl 2-benzyl-3-methoxy 3-thioxopropanoate	C ₁₂ H ₁₄ O ₃ S	238	13.607	6.98

α -calcorene (4.94%), α -muurolol (4.90%), D-germacrene (4.84%), d-cadinene (4.48%), isolede (3.99%) and α -muurolene (2.33%) (Table 4). The methanolic fraction of *C. zeylanicum* comprised of cinnamic acid (22.71%), 5-methylamino-1,3,4-thiadiazole-2-one (18.29%), α -muurolol (16.11%), 1-phenylpropene-3.3-diol diacetate (14.34%), 1H-indazole, 3-methyl (12.52%), 1-methyl 2-benzyl-3-methoxy-3-thioxopropanoate (6.14%), 4-propylbenzoyl chloride (4.23), α -copaene (2.59%) and d-cadinene (2.52%) (Table 5). The active ingredients of *C. zeylanicum* ethyl acetate extract revealed the presence of a high proportion of 1-phenylpropene-3.3-diol diacetate (68.56%) followed by eugenol (11.67%), cinnamic acid (8.22%), *o*-Methoxy cinnamaldehyde (6.10%), and 6-ethyl-3,4-dimethylphenol (5.45) (Table 6). The diethyl ether extract comprised of δ -cadinene (30.97%), α -muurolene (24.22%), eugenol (23.98%), 1-phenylpropene-3.3-diol diacetate (10.99%), 1-methyl 2-benzyl-3-methoxy-3-thioxopropanoate (6.98%) and α -copaene (2.85%) as the major active ingredients (Table 7).

The potent anticandidal activity of *C. zeylanicum* extracts is due to the high content of essential oils, which alters the cell membrane through inhibition of ergosterol

synthesis leading to the leakage of cellular contents such as intracellular ions and proteins²⁸. An earlier study reported that the disturbance in fungal metabolism by reducing the activity of malate dehydrogenase and succinate dehydrogenase in tricarboxylic acid cycle can be an important mode of fungicidal action against *Candida* pathogens²⁹. The active components such as cinnamaldehyde^{30,31}, eugenol^{32,33} and T-muurolol³⁴ were previously reported to exhibit antifungal activity. Further, the active components of cinnamon extracts such as eugenol, cinnamic acid and cinnamaldehyde have been reported to act synergistically to exert antimicrobial activity³⁵. The potent antifungal activity of *C. zeylanicum* ethyl acetate extract may be due to the presence of high amounts of phenylpropene derivatives (68.56%), which are known to disrupt cell membrane fluidity, integrity and permeability³⁶. Cinnamaldehyde, which is found in the ethyl acetate extract of *C. zeylanicum*, is reported to exert antifungal activity against *Candida* pathogens through inhibition of both chitin synthase and β -1,3-glucan synthesis, which are responsible for synthesizing the cell-wall components³⁷. Hence, the present study demonstrates the basis for enhanced antifungal activity of ethyl acetate

extract compared to other *C. zeylanicum* extracts. In this study, eugenol was detected in the ethyl acetate (11.6%) and diethyl ether (23.9%) extracts of *C. zeylanicum*. Eugenol is a phenolic compound that acts as an antifungal agent due to its role in the disruption of cell-membrane permeability³⁸. Other studies have reported that sesquiterpenes such as caryophyllene and α -copaene, which have been detected in essential oils of different plants, act as potential antifungal agents against *Candida* pathogens^{39,40}. This is an agreement with the results of this present study, where α -copaene was detected in the diethyl ether (2.85%) and methanolic (2.59%) extracts of *C. zeylanicum*, while isocaryophyllene (13.9%) was found only in the *n*-hexane extract.

C. zeylanicum extracts showed high antimicrobial potency against common candidal strains causing vaginitis. Ethyl acetate extract of cinnamon exhibited the highest antifungal activity against different *Candida* pathogens. Antifungal activity of ethyl acetate extract of cinnamon was significantly higher than that of terbinafine. High anticandidal activity of cinnamon ethyl acetate extract at low concentration (500 μ g/disc) makes it a potential source for the production of natural antifungal drugs. It can also be potentially effective against the drug-resistant *Candida* strains. Thus, *C. zeylanicum* extract can be used as a safe antifungal agent for treating VVC in pregnant women.

Conflict of interest. The authors declare that there is no conflict of interest.

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First record of circa 970 Ma post-collisional A-type magmatism in the Sendra Granitoid Suite, central Aravalli orogen, northwest India

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This study provides the first record for the emplacement of post-collisional A-type granites in extensional regime during the late Grenvillian period in northwest India. The ca. 970 Ma granites of the Sendra Granitoid Suite (Chang pluton) intrude calc-silicate rocks of the South Delhi Supergroup in the central Aravalli orogen. The Chang pluton is composed of granite *sensu stricto*; the granites are metaluminous, ferroan, calc-alkalic, and are characterized by high Ga/Al (>2.5), Nb + Y (>60 ppm), Ta + Yb (>6 ppm), REE, HFSE and zircon saturation temperatures, typical of A-type granites. The Y/Nb >1.2 further classified the rocks as A₂-subtype, signifying their derivation from crustal sources in a post-collisional setting. The crustal source is also supported by their high LILE (Rb, K and Ba), and Pb, Th and REE. The geochronological data and tectonics of the region indicate that the granites were emplaced about 30 Myr after the Grenvillian collisional orogeny. This scenario likely resulted due to delamination of the lower part of the thickened orogenic lithosphere. These results are expected to have significant implications for the assembly tectonics of the Rodinia supercontinent.

Keywords: A-type granites, post-collisional extension, whole-rock geochemistry, magmatism.

THERE is a broad consensus that the amalgamation of the Rodinia supercontinent took place between 1300 and 900 Ma (refs 1 and 2). The position of India in Rodinia, however, remains enigmatic. Some consider that India was not a part of Rodinia³, while others are of the view that India was located west of Australia⁴. Further, it has also been proposed that the Eastern Ghats Mobile Belt (India) and the Rayner Province (East Antarctica) were attached by 990–900 Ma, and India broke away from Rodinia by 750 Ma (ref. 1). Like the Central Indian Tectonic Zone (CITZ) in central India, the northern and central parts of the Aravalli orogen (northwest India) also show imprints of the Grenvillian orogeny at 1085–930 Ma (refs 5 and 6).

In the central Aravalli orogen, the region about 10 km south of Beawar (Figure 1) experienced the late Grenvillian

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