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A MINI REVIEW: MEDICINAL PLANTS FOR TYPHOID FEVER IN INDONESIA

LELIMISKA IRMADANI SYARIF [1], ADE RIFKA JUNITA[1], MOCHAMMAD HATTA[1*], RESSY DWIYANTI[1,2], CAHYONO KAELAN[3], MUHAMMAD SABIR[1,2], RIZKI AMELIA NOVIYANTHI[1,4] , MUHAMMAD REZA PRIMAGUNA[5], NUR INDAH PURNAMASARI[6]

[1]Molecular Biology and Immunology Laboratory, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Department of Medical Microbiology, Faculty of Medicine, Tadulako University, Palu, Indonesia
[3]Department of Pathological Anatomy, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[4]Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[5]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[6]Department of Obstetrics and Gynecology, Faculty of Medicine, Halu Oleo University, Kendari, Indonesia

***Correspondence authors:** Prof. Mochammad Hatta, M.D, Ph.D, Clin Microbiologist (Cons)
Molecular Biology and Immunology Laboratory, Faculty of Medicine, University of Hasanuddin, Jl. Perintis Kemerdekaan KM.10, 90245. Tel/Fax: 062-0411-586010.
Makassar, INDONESIA.
Email: hattaram@yahoo.com
ORCID: https://orcid.org/0000-0002-8456-4203

ABSTRACT

Nature is currently one of the medicinal agents used for treatment of some diseases, such as typhoid fever. The increasing number of antibiotic resistance strains has prompted researchers to find new modes of therapy for these diseases. Patients who suffer resistance to antibiotics need longer time for hospitalization to recover from that disease. Some studies focus on traditional therapy using plants, not only for typhoid fever, but also other infectious and metabolic diseases. According to the literature, there are 32 plants that have antimicrobial effect, anti-inflammatory, bactericidal, and phagocytic stimulation effects for *Salmonella typhi* which can be used as an alternative therapy for typhoid fever. All of the plants are found in Indonesia such as *Punica granatum*, *Carica papaya, Cocus nucifera, Cymbopogon citratus, Mangifera Indica, Solanum lycopersicum, Solanum nigrum, Manilkara zapota, Myristica fragrans, Cymbopogon citratus, Citratus aurantifolia, Momordica charantia, Moringa oleifera, Luffa acutangula, Aloe vera, Psidium guavaja, Allium sativum, Occimum gratissimum and Apium graveolens L.*

Keywords: Typhoid fever; Medicinal Plants; *Salmonella typhi*

Correspondence:
Prof. Mochammad Hatta, M.D, Ph.D, Clinc Microbiologist (Cons)
Molecular Biology and Immunology Laboratory, Faculty of Medicine, University of Hasanuddin, Jl. Perintis Kemerdekaan KM.10, 90245. Tel/Fax: 062-0411-586010.
Makassar, INDONESIA.
Email: hattaram@yahoo.com
ORCID: https://orcid.org/0000-0002-8456-4203

INTRODUCTION

Typhoid fever is an infectious diseases caused by gram-negative bacteria, *Salmonella typhii* , with the most common clinical manifestations in the form of fever, dizziness, nausea, vomiting, decreased appetite, abdominal pain, constipate or sometimes diarrhea and coated tongue with different clinical stage of the disease. Such symptoms could be considered mild to moderate [1]. The spread of typhoid disease can only be transmitted from human to human. A human carrier can easily transmit dormant germs in the intestine to others with contamination through drinks or food that comes into contact with patients or who have been infected with typhoid [2-4]. Diagnosis of typhoid in a patient is collaborated from history taking, symptoms and laboratory findings from blood, urine, or feces. Methods for diagnosing typhoid fever have been well-developed at a global level. Some studies have been tried and found one of the diagnostic test for typhoid fever by OMP latex with 95.65% of sensitivity and 50% of specificity but an adjuvant treatment for typhoid from plants has yet to be discovered [5].

Prevalence of typhoid is still an issue. The highest incidence of typhoid is> 100 / 100,000 cases per year in South-Central Asia and South-East Asia [6,7]. In Indonesia, based on study conducted by Leon R et all', in 2008, the average age group was 81.7 per 100,000 per year with an incidence rate of 148.7 in 2-4 year age group, 180.3 for the 5-15 year age group, and 51.2 per 100,000 per year for more than 16 years age with an average age of 10.2 years [8-10]. Highlighted that the risks factor of typhoid depend on family conditions, such assanitation, availability of clean water, individual hygiene habits, knowledge of the prevention and the spread of typhoid [11,12]. Along with the high incidence of typhoid fever, particularly in Indonesia, research on the management of typhoid fever both medical and non-medical has also increased. Since 2001, especially in South Sulawesi, the number of antibiotic resistance for typhoid therapy is reported to be very low (tetracycline 1.34%, amipicillin 1.87%, Chloramphenicol 1.04%, Ciprofloxacin 0.11%, MDR 1.21%), respectively increasing through 2007 to 8.13%, 7.96%, 7.84%, 3.90%, 6.83% [13]. Despite this increase, Chien Shun (2014) found that the level of antibiotic resistance for *Salmonella typhi* in Indonesia is still relatively low in Asia compared to Bangladesh, Taiwan, and Vietnam [14]. In Indonesia some researchers have focused their study to discover other plants that can be used as medicinal therapy not only for infectious disease but also metabolic disease. Titus et al. (2018) found that orally red fruit (*Pandanus conoideus*) act as an immunomodulator for Human Immunodeficiency Virus patients with antiretroviral therapy [15]. In a second case of acute toxoplasmosis, extract of *Curcuma longa* has anti-toxoplasmosis immunoglobulin G and immunoglobulin M [16,17]. *Plectranthus scutellarioides* and *Coleus scutellaroides* extract also has a good response as therapy for *Candida albicans* infection [18,19]. Tawali et al. (2019) also concluded that extract of Buni-Berry (*Antidesma bunius*) is effective in increasing PON1 expression in BALB/c mice fed with high fat diet [20]. Considering this condition, several studies are trying to bring their study to medicinal herbs or medicinal plants for typhoid management. As such, some plants in Indonesia can be extracted and then used as an antimicrobial agent particularly in destroying *Salmonella typhi* bacteria [21]. Previous study revealed that *Thalassia hemprichii* contains bioactive compounds that have the potential to be antibacterial and antioxidant [22-23]. Other study, in traditional medicine such as snakehead fish (*Channa striata*) can increase serum albumin levels in patients after surgery [24].

INDONESIAN ANTI-SALMONELLA OF MEDICINAL PLANTS

Even though there are antibiotics that are sensitive to *salmonella typhii,* the level of resistance to other types still exist and total of case more increasing nowdays [25-27]. Likewise, the use of anti-typhoid vaccine as a preventive to high morbidity and mortality of typhoid has been widely used, but there are still limitations to it. Table 1 describes several types of plants that have been studied and proven to have anti-salmonella effects and can be used as herbal therapies for typhoid. Of the 32 types of plants that have been studied, these Indonesian typical plants which can be used as herbal therapy for typhoid cases. The majority of antimicrobial activity was assessed from the amount of inhibition zone on medium that had been provided using the MIC (*Minimum Inhibitory concentration)* test system [28]. Some research on herbs also compares the antimicrobial activity of the antibiotics as used for medicinal therapy to treat typhoid [29-33]. Last study in Indonesia conclude that Miana Leaves (*Coleus scutellaroides.* L) extract also gave a significantly effect treatment in Balb/c mice induced by *Salmonella typhi*. The result showed that there was a different pattern of TLR-4 Expression. There was a decrease in TLR-4 mRNA expression from Miana leaves extract treatment group and the mixed of antibiotic [34].

In *Azadirachta indica* , the zone inhibition of acetone and ethanolic stem bark extracts produced more effective results as compared to other extracts, including comparison with the common antibiotic such as amoxicillin, cotrimoxazole, cefotaxime, ceftriaxone, ciprofloxacine, and chloramphenicol with diameter zone ranges from 18-35 mm and 15-31mm [35]. Rani.P et al. (2004) categorized antimicrobial activity against *Salmonella* typhii on *extracts* of *Aegel marmelous, Punica granatum,* and *Myristica fragrans fruit* as strong antimicrobial with an inhibition zone of ≥9-15mm while *Cichorium intybus, Solanum ningrum, Apium graveolens, Ocimum sanctum* as moderate antimicrobial with an inhibition zone of ≥5-9mm [36]. A study conducted by Nkanwen (2009) proposed that *Crinum purpurascens* had bactericidal effects. The bactericidal or bacteriostatic categorization is based on MBC / MIC ratio. If the ratio is ≤ 4 it is categorized as a bactericidal agent; if it is > 4 it is categorized as bacteriostatic [37,38]. It is slightly different from water extract of *Houttuynia cordata* (HCWE) in its antimicrobial activity. These data suggest that HCWE is stable and beneficial in the treatment of bacterial infection including intracellular replicating pathogens [39,40].

In Cameroon, Roger et al. (2015) screened several potential plants to have antibacterial activity against *Salmonella*, one of the plants is *Bidens pilosa* [41,42]. This plant has antibacterial activity against *Salmonella* bacteria with the optimal inhibitory zone of 12.5 ± 0.4 mm at a concentration of 80mg / ml in the leaf extract using chloroform. Chemical constituent of *Bidens pilosa* are flavonoids, phenylacetylens, alkaloids, steroids, triterpenoids and tannins, satureted carbohydrate, aliphatic carboxylic acid, acetylenic 38 hydrocarbons, phenols, chalcons, flavonols, porphyrines [43,44]. Peter et al. (2014), in his research stated that *Carica papaya* has the strongest antibacterial activity potential in the leaf extract using chloroform with concentration of 100 mg / ml with an inhibition zone that formed 8.8 mm compared to other bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa,* and *E.*coli [45]. Phytochemicals of *Carica papaya* with ethanol extracts such as alkaloids, saponins, flavonoids and glycosides contains magnesium, potassium, calcium and iron [46-48]. *Cocos nucifera* also has the higher antibacterial activity of the extract diethylether compared to other solvents extracts with inhibition zones formed 20 ± 0.5mm, even though also obtained the antibacterial activity of the extract against bacteria *E.*coli [49-53]. Comparing efficacy of *Cymbopogon citratus* and *Carica papaya* as enteric fever therapy agist *Salmonella* in Bayelsa State and found that *C. citratus is* more effective against *Salmonella typhi* than *C.papaya* with inhibition zones in *Salmonella typhi* 22.67 ± 0.88 mm, *S.paratyphii* 22.33 ± 1.03mm, and *S.typhimurium* 21.17 ± 1.37 mm . In *C.papaya* the largest inhibition zone was 21.18 ± 0.88 mm in *S.paratyphi* bacteria [54]. *Cymbopogon citratus* contains some phytoconstituent such as flavonoids, phenolics, terpenoids, tannins, alkaloids and essential oils [55]. In other studies, *Mangifera indica* also has antibacterial activity of ethanol extract which has no critical different effect compared to medical therapy [56]. Musa et al. still concluded that *M.indica* can be an alternative therapy for typhoid cases with zone of inhibition formed at a concentration of 100mg / ml is 18mm better than amoxicillin and chloramphenicol, which has a zone of inhibition formed at the same concentration of 17mm and 12mm for each, although gentamycin still exhibits better results with 25mm inhibition zone [57]. This is because the phytochemical composition of mango leaves consists of alkaloids, phenols, flavonoids, sapponins, tannins and contains minerals calcium, magnesium, potassium, phosphorus and sodium which are considered to have a role as antioxidants, anti-inflammatory and immunomodulators [58-59]. *M.indica* is a potential medical plant as antimicrobial, anti-cancer, cardio and radio protective, and recognition of memory [60]. In vitro investment of efficacy of some antibitoics and *Mamordica charantia* extract to find the stronger antimicrobial against *S. typhi* shows that *M. chantia* has the therapeutic potential as a typhoid fever treatment. When compared with Ampicillin, Chloramphenicol, gentamicyn, tetracycline and other types of antibiotics, *M.charantia is* more sensitive to *S.typhi* when considering it's zone of inhibition which reach 14mm, and not significantly different from ciprofloxacin with 16mm inhibition zone [61-62]. In addition Adeyi et al. also histopathologically assessed the features of hepatocytes that had received herbal therapy for lemongrass leaf extract in mice and the results showed that there was a gradual recovery from hepatocyte cells in the liver when compared to those which not receiving herbal therapy [63]. Another study conducted in Nigeria by Etuk et al. assessed the effect and toxic dose of *Psidium guajava* extracts *against* mice infected with *Salmonella typhi* . The result demonstrated that giving 20-30mg/ 100g of guava extract will improve the clinical symptoms, especially fever. In comparison with giving 2.5mg/100g of mice body weight, the results of clinical symptoms improvement were the same as giving 30mg/100g whereas on the 2nd day the condition became normal without any fever and after being observed until the seventh day the temperature remained stable. At a dose of 40mg-50mg / 100g side effects emerge in the form of behavioral changes such as insomnia and irritabilaity but will not cause death [64-67]. Flavonoid in *Psidium guajava* is assessed to have antibacterial activity against *Salmonella enteriditis* with MIC 200 μ g / ml [65]. Purba et al (2018), also assessed the effect of extract of *Solanumlycopersicum* provision to *Salmonella typhi.* These studies concluded that there are differences in inhibitory zones formed at each difference concentration of *S. glycopicicum* . Maximal inhibition zone was formed at a concentration of 100% with the average of 32.67mm and is still low compared to the positive control using ceftriaxone with 48, 33 mm [68]. *Zingiber officinale* is also one of the plants that can be used as medicine for typhoid [69]. This is in accordance with the Oluduro study which assessed the antibacterial activity of *Z.officinale*, *Allium Sativum and Momordica charantia* through methanol, ethanol and aqueous extracts. The results showed that there was antibacterial activity on the *Z.officinale* methanol extract with inhibitory zones formed 5.4 mm at extract concentrations of 50 mg / ml and did not have an effect on the lower concentration [69]. *Allium sativum* gives the highest inhibitory zone in methanol extract with a concentration of 50 mg / ml inhibition zone formed 6.3 mm, while *M. charantia* is the largest inhibition zone on 11 mm on aqueous extract at the same concentration. The higher the concentration, the greater its inhibitory zone will be formed, however, there is no further research related to the toxic dose of this plant [70]. Crude extract of *Allium sativum* can also be used as an alternative antebacterial in *Salmonella*. This has been proven by Adebolu et al. (2011), with a diameter of inhibition zone that formed 23.8mm which is 0.2mm with streptomicyn 24.00mm while gentamycin 22mm, chloramphenicol 20mm, ofloxacin 19.5mm and erythromycin 16mm [70]. Another study conducted by T.Ayogu (2008), assessed the combination of raw extract of garlic and ginger as a treatment for typhoid to be sensitive at 0.8g / ml concentration as antibacterial therapy even though the inhibitory zone formed was smaller than 20mm compared to 30mm chloramphenicol as the controler [71].

In contrast to the above studies that assessed antibacterial activity in medical plants based on the formed inhibitory zones, Susanti R. et al. in her study tried to assess the effect of giving *Alloe vera* as an immunomodulator for ROS activity of macrophages in mice infected with *S.typhimurium*, which is one of the typhoid-causing bacteria [72]. The results revealed that administering *A.vera* has a significant effect on increasing ROS macrophages production in mice, however, further research is needed regarding NO and cytokines involved in immune response to *Salmonella* bacteria [73-74]. In line with this study, flavonoids, phenols, vitamins C and E were considered capable of reducing perioxidative damage by decreasing levels of monocine TNF-α, IL-1, and IL-6 [75].

In the study conducted by Natarajan (2005), apart from rootstock extract, leaf extract also has antibacterial activity with inhibition zone formed by 11 mm using methanol in *Salmonella typhii* A [76]. S. Marasini et al.(2015) also assessed some fruits and vegetables that have strong antimicrobics that are considered to have antibacterial activity against several microbes, including *Salmonella typhi* based on the formed zone of inhibition [77]. In *Mangifera indica, the largest* inhibition zone formed in the methanol extract of 12 mm compared with Hexane, choloroform, acetone extract [78]. In *L. Acutangula* n-hexane extract gives the larger inhibitory zone compared to other solvents with an inhibition zone formed 9mm, the inhibition zone formed on the same chloroform and acetone extract, that is 7mm [79]. Doughari(2007), *Moringaoleifera* also had lower antimicrobial activity on leaf extract using acetone compared to ethanol extract and was able to form a 7 mm inhibition zone on acetone extract and 8 mm with ethanol at a concentration of 100 mg / ml [80-85]. *Manilkara zapota* also has antibacterial activity including *Salmonella typhi* on stem bark and leaves extracts using ethyl acetate solvent. However, the result of the formed inhibitory zone is still lower compared to kanamycin [86-87]. In addition to *Manilkara zapota*, *Ocimum gratissimum* also has antibacterial activity against *Salmonella* [88-91]. Other plants like *Solanum nigrum* was analyzed the phytochemical and its effect as an antimicrobial against *Salmonella typhi,* and the results of that study indicated capablaity of managing typhoid fever, paratyphoid fever, salmonellosis and other nosocomial infections [92-94]. Phytochemical composition of liquid samples from *S.nigrum* consist of Sapponins, tannins, sterols, cardiac glycosides, flavonoids, terpenoids, alkaloids, and phenolic compounds [95-97]. Like *S.nigrum, Apium gravelens* also has antibacterial activity compare with gentamycin. Shown by alcoholic extract of *A.gravelens* in 25 ° C with 200mg / ml the mean inhibition zone is 15 ± 0 Ad and in 37 ° C with the same concentration inhibition zone mean ± 0.5 Ad is 14:33 but still less than inbition zone of gentamycin with 17.3 ± 0.17 Ae [98,99]. A study from Nandagopal et al. (2007) also shows that root extract of *Chicorium intybus L* antibacterial effect aginst *Salmonella typhi* with maximum inhibition was observed with hexane solvent (19.2 ± 0.43mm). This result is better than inhibition zone of chloramphenicole with inhibition zone is 14 ± 0.23 mm as a control [100]. Ibukun et al. (2007), evaluates antimicrobial of *Citrus aurantifolia* for *Salmonella typhi* from aqueous extract with inhibition zone of 21 mm less than ciprofloxacin with 30 mm [101]. *Terminallia belerica* also has anti- *Salmonella* activity. Compare with other plants such as *Z.officinalis, A.recemosus, P.kurroa* and *V.vinefera, T.belerica* have the highest diameter of inhibition zone with 20.0 + 0.9 mm [102].

MATERIALS AND METHODS

This study, compare to other literature from many research focuse on finding plants as a therapeutic agents from natural sources for the treatment of typhoid. Some studies related medicinal plants had been published to be safe, less side effect and efisien for treating the diseases. This review was composed by literature searching on medicinal plants for typhoid fever in other country from the databases PubMed and Google Scholar with the keywords included “Salmonella typhi”, “Typhoid fever”, “Herbal Medicine”, “Medicinal plants for typhoid fever”, “anti-salmonella activity of plants”, “antibiotics resistence for typhoid fever” etc.

CONCLUSION

The phytochemical functions of some plants have been discovered, but the phytopharmaceutical benefits of other plants need to be studied, especially plants in Indonesia as potential treatment for typhoid fever. Flavonoids are the most phytochemical of the plants and have an antimicrobial effect for bacteria caused typhoid fever. There are 32 plants in Indonesia with antimicrobial effects that can be used as medicinal therapy for typhoid fever.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

Table 1. REVIEW OF INDONESIAN MEDICINE PLANTS IN ANTI SALMONELLA

No.	Plants	Local Name	Uses	Extraction	Effects	MIC	Zone Inhibition	Reference
1	Azadirachta indica	Buah Mimba	Bark	Ethanol & Methanol	Growth inhibition of bacterial on medium DPPH radical Scavenging Lipid Peroxidation	NM	20-25mm	35,103
2	Aegel marmelous	Buah Maja	Fruit Pulp	Methanol	Strong antimicrobial agent	≥256 µg/mL	≥9-15mm	36,104
3	Punica granatum	Buah Delima	Dried fruit peel	Methanol	Strong antimicrobial, antidiarrheal	≥32µg/mL	≥9-15mm	105
4	Myristica fragrans	Buah Pala	Fruit	Methanol	Strong antimicrobial	≥64µg/mL	≥9-15mm	27,30, 36
5	Crinum purpurascens	Lili Jawa	Leaves	CH2Cl2/OH	Bactericidal	6mg/mL	25mm	37-38
6	Houttuynia cordata	Tanaman Pangkal Racun	Powder	Water	Phagocytic stimulation effect	NM	NM	39-40
7	Bidens pilosa	Ketus	Leaves	NM	Against typhoid fever	512µg/mL	12.5 ± 0,4 mm	41,43-44
8	Carica Papaya	Pepaya	Leaves	Chloroform	Potential Natural antibacterial compounds	NM	8.8mm	45-48, 54, 106
9	Cocus nucifera	Kelapa	Crude	Diethyleth er	antibacterial against s.typhii with high zone of inhibition	NM	20±0.5mm	49-52
10	Cymbopogon citratus	Serai	Leaves	Ethanol	highest zone inhibition as antibacterial against s.typhii	5-50mg /ml	22.67±0.88	53-55, 107-109
11	Mangifera Indica	Mangga	Leaves	Ethanol	antimicrobial activity against s.typhii	100mg/ml	18mm	56,58-60,110

12	Momordica charantia	Peria / Pare	Leaves	Methanol	potent antimicrobial agents against S.typhii	NM	14mm	61-62, 69
13	Psidium guajava	Jambu Biji	Leaves	Water Extract	ability to treat the clinical symptoms of salmonella infection in rats	NM	NM	63-67
14	Solanum lycopersicum	Tomat	Fruit	Ethanol	Growth inhibition of salmonella typhi	NM	32.67mm	68, 111
15	Zingiber officinale	Jahe	Leaves	Methanol	low activity against s.typhii	1.0mg /ml	5.4mm	69
16	Aloe vera	Lidah Buaya	Leaves		Immunostimulator, Increase activity of macrophage and monocyte t (in vitro), activated ROS (in vivo)	NM	NM	74,75
17	Allium Sativum	Bawang Putih	Raw	Water	Produce higher antimicrobial	0.01 %	23.8mm	69,70, 112
18	Euphorbia fusiformis	Patikan Kebo	Root stock	Acetone	Antimicrobial agent s.typhii	NM	12mm	76
19	Lagenaria siceraria	Labu air	Fruit Peel	Aqueous	Antimicrobial agent s.typhii	>1250μg/ml	±17mm	113-116
20	Solanum tuberosum L	Kentang	Fruit Peel	Chloroform	Antimicrobial agent s.typhii	NM	9mm	77-78
21	Ananas comous	Nanas	Fruit Peel	Chloroform	Antimicrobial agent s.typhii	NM	9.3mm	77
22	Luffa acutangula	Gambas	Fruit Peel	Methanol	Antimicrobial agent s.typhii	NM	9mm	77,79,117
23	Ocimum sanctum	Kemangi	Leaves	Ethanol	Antibacterial activity	250-500μg/ml	11-13mm dan 16-24mm	118-122
24	Moringa oleifera	Kelor	Leaves	Ethanol	Antimicrobial agent	8mg/ml	8mm	80-85
25	Manilkara zapota	Sawo	Leaves Stem bark	Ethyl acetate	Antibacterial Activity	512μg/ml 256μg/ml	9mm 12mm	86,87
26	Occimum gratissimum	Selasih Mekah	Leaves	Water Extract	Antimicrobial agent and antidiarrheal	0.1%	26 mm	88-91
27	Solanum nigrum	Ranti/ Leunca	Plants	Methanol	Antimicrobial	0.50g /ml	NM	92-97
28	Apium graveolens L	Seledri	Plants	Ethanol	Antimicrobial agent	200mg/ml	14.33-15mm	98-99
29	Cichorium intybus	Semak Menahun	Roots	Hexane	Antimicrobial	100μg/ml	19.2±0.43 mm	100
30	Citrus aurantifolia	Jeruk Nipis	Fruit	Aqueous	Antimicrobial agent	512mg/ml	21mm	101, 111
31	Terminalia belerica	Pohon rimba	Fruit	Water extract	Antisalmonella agent	12.5 mg/ml	20.0+0.9mm	102
32	Glycyrrhiza glabra	Akar Manis	Seed	Methanol	Antimicrobial activity			103

NM: Not mentioned

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