Research Article

Polyherbal Formulation to Treat Diarrhoea

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ABSTRACT

Formulations containing two or more than two herbs are called polyherbal formulation. The conception of polyherbalism is specific to Ayurveda albeit it is arduous to explain in term of modern limitations. Historically, the Ayurvedic literature "Sarangdhar samhita" focus the slant of synergism behind polyherbal formulations. Even though single herb formulation have been well entrenched due to their active phytoconstituents, they usually present in minute amount and sometimes they are insufficient to actualize the desirable therapeutic effects. Medicinal plants have been used as popular treatments for numerous human diseases for thousands of years. Universality of polyherbal formulation is due to their high effectiveness in a ample number of diseases. Diarrhoeal diseases endure to be a leading cause of morbidity and mortality throughout the world and there is revived interest in the revelation of novel compounds that can be used to bout these diseases. Numerous studies have endorsed the traditional use of anti diarrhoeal medicinal plants by investigating the biological activity of extracts of such plants, which have antispasmodic effects, delay intestinal transit, suppress gut motility, stimulate water adsorption or reduce electrolyte secretion. Of the numerous phytochemicals (such as alkaloids, tannins, flavonoids and terpenes) extant in active extracts, tannins and flavonoids are thought to be culpable for anti-diarrhoeal activity by booming colonic water and electrolyte reabsorption. Others exploit by inhibiting intestinal motility.

Keywords: Diarrhoea, medicinal plants, phytochemicals, alkaloids, flavonoids, phenolics, tannins.

INTRODUCTION

Despite advances in the empathetic of the causes, treatment and prevention of diarrhoeal diseases, an approximated 4.6 million people, including 2.5 million children, die from diarrhoea every year, peculiarly in developing countries. The World Health Organization construe diarrhoea as three or more loose or watery stools in a period of 24 h, although changes in the viscidity of stools are important beacon of disease.[1] Diarrhoea can be classified as acute or chronic, with acute diarrhoea being the most probable form. Acute diarrhoea has an hasty onset, resolves within about 14 days and is usually caused by an infectious agent, although drugs, poisons (including bacterial toxins) or acute inflammatory reactions can accord.[2]

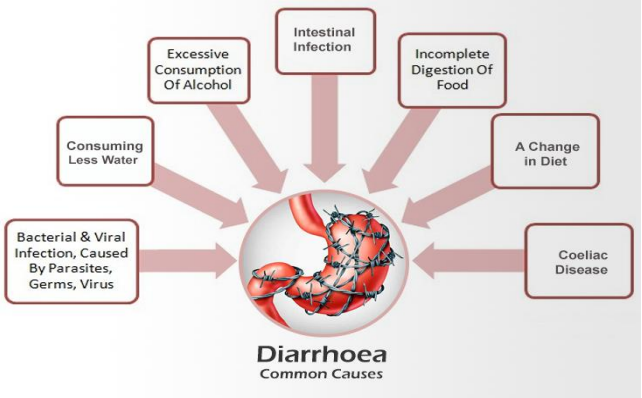

Figure 1: Common causes of Diarrhoea

Worldwide, rotavirus is the main cause of infectious diarrhoea, particularly among young children, however, other viral (adenovirus, enterovirus and norovirus), bacterial (Escherichia coli, Salmonella, Shigella, Campylobacter and Vibrio cholerae) and parasitic (Cryptosporidium and Giardia) agents are exigent pathogens.[3] Oral rehydration therapy (ORT) remains the major treatment for diarrhoea, although it does not deflate the volume or duration of diarrhoea.[4] Other treatment options entail antibiotics and gut motility suppressing agents, which aim to reverse dehydration, snip the length of illness and recede the period of time an individual is infectious.[5] Treatment with pharmacological agents that are pathogen-specific or that muffle severe symptoms would be of asset to patients suffering from prolonged diarrhoea.[6] There have been copious reports of the use of doctrinal plants for the treatment of diarrhoeal diseases. Many plant-derived medicines used in traditional African, American, Asian, European and other indigenous medicinal systems have been documented in pharmacopeia's as agents used to treat diarrhoea. The bourn of this review is to present some recent examples of studies that have dealt to ratify the traditional use of medicinal plants with specific biological activity. In particular, traditional medicinal plant extracts or phytochemicals that have been set out to abate the symptoms of diarrhoea will be discussed. In addition, studies that have investigated the vein of anti-diarrhoeal action and the asylum of plant-derived medicines will be described.

TRADITIONAL MEDICINAL PLANTS WITH DEMONSTRATED ANTIDIARRHOEAL ACTIVITY: PHYTOCHEMICAL ANALYSIS AND MODES OF ACTION

The plants elucidated below have been constituted as treatment for diarrhoea on the basis of their dexterity to prevent or improve diarrhoeal symptoms induced in experimental animals or, where tested, in clinical trials in humans. Phytochemical analysis of plant preparations and the identification of active components therein have helped to explain the mechanism of anti-diarrhoeal activity. Assimilation of plants with verified hustle is the first phase in the discovery of lead compounds that may be advanced into novel therapeutic agents. Traditional medicinal plants used in India are the roots of *Jatropha curcus* (Euphorbiaceae) are used traditionally in the western coastal areas of India to clout dysentery and diarrhoea.[7] Methanol extracts have displayed dose-dependent inhibition of castor oil-induced diarrhoea and intraluminal fluid accession, as well as small intestinal transit. The extracts may act by inhibiting prostaglandins and reducing small intestinal impellent movement. In a similar manner, [8] is the medicinal plant, *Calotropis gigantea* (Asclepiadaceae). Water: ethanol (50:50) extract produced a statistically significant abatement in the rigor and frequency of diarrhoea produced by castor oil. In addition, both castor oil-induced intestinal fluid accumulation and intestinal volume content were subdued significantly. Numerous phytochemicals, including sugars, flavonoids, flavonol glycosides and terpenes, have been spotted in this plant and these may umpire the anti-diarrhoeal properties, although the active component has not been entitled. An ethanol extract of the root of *Trichodesma indicum* (Boraginaceae), another Indian medicinal plant used to treat diarrhoea, has been found to reduce castor oil-induced enter pooling and the thrust of a charcoal meal in experimental animals.[9] Similarly, a chloroform extract of the roots of *Aegle marmelos* (Correa), a medicinal plant used in India, Burma and Sri Lanka for a variety of malady, including diarrhoea, spread out significant activity against castor oil-induced diarrhoea which was tantamount to the anti-diarrhoeal agent, loperamide. [10]

Figure 2: Different Plants showing Anti-Diarrhoeal Activity

It has been explored that the acreage of *Aegle marmelos* (unripe fruit), along with three other indigenous Indian medicinal plants including *Acorus calamus* (Araceae), *Pongamia glabra* (Leguminosae) and *Strychnos nux-vomica* (Loganiaceae). The methanol extracts of all plants were more astir than aqueous extracts in contrast to castor oil-induced diarrhoea in mice and significantly abridged the total weight of faeces, although *Strychnos nuxvomica* was baneful at high doses. *Jussiaea suffruticosa* (Onagraceae) is a well-known historic medicine in India, where the whole plant is condensed to pulp and steeped in buttermilk as a treatment for dysentery and diarrhoea. [11] An extract of this plant has been shown to bridle castor oil-induced diarrhoea, enter pooling and gastrointestinal motility. In animal studies, the drift and acerbity of diarrhoea as well as the prevalence of defaecation and wetness of faecal droppings were reduced and these effects were comparable to those espied for standard antidiarrhoeal drugs. These effects may be the aftermath of tannins present in plant extracts.

POLYHERBAL FORMULATION

Scientific studies have concede that these plants of waffling potency when combined may theoretically produce a terrific result, in comparison to individual use of the plant and also the entity of their individual effect, thus positive herb-herb interaction produce synergism,

which could be pharmacokinetic synergism or pharmacodynamic synergism. Adoration of polyherbal formulation is due to their high effectiveness in a tremendous number of diseases. They have wide restorative range (effective at low dose and safe at high dose), fewer side effects, eco-friendly, cheaper and readily available polyherbal formulations are not always snug. As described in Charaka Samhita, Ayurvedic formulations have adverse effect when rigged or used inappropriately. The problems of polyherbal formulation occur due to sources and manufacturing process, patients, Ayurvedic practitioners, drug-herb interaction, clinical reproducibility, toxicity due to ludicrous manufacturing and irrational prescribing of polyherbal formulation as well as law and regulations. In spite of all these scrape, popularity of polyherbal formulation is piling up and hence it claim more scientific search in this field.[12]

PHYTOCHEMICAL CONSTITUENTS OF LEMON AND TEA POWDER USED IN TREATMENT OF DIARRHOEA

I. Lemon:

The lemon, *Citrus Limon* (L.) Osbeck is a stripe of small evergreen tree in the flowering plant family Rutaceae, native to South Asia, primarily North-eastern India.[13] The tree's ellipsoidal yellow fruit is used for culinary and non-culinary intendment throughout the world, primarily for its juice, which has both culinary and cleaning uses. The pulp and rind (zest) are also pre-owned in cooking and baking. The juice of the lemon is about 5% to 6% citric acid, with a pH of about 2.2, giving it a sour taste. The weird sour taste of lemon juice makes it a key ingredient in drinks and foods such as lemonade and lemon meringue pie. [14] Lemons are a rich source of vitamin C, providing 64% of the Daily Value in a 100 g dollop. Other prerequisite nutrients, however, have irrelevant content.[15] Lemons contain umpteen phytochemicals, including polyphenols, terpenes and tannins. The ubiety of flavonoids, alkaloids, steroids, terpenoids, saponins, cardiac glycosides, and reducing sugars in all the juice concentrates studied endorsed that citrus fruits are affluent sources of phytochemicals.[16]

Table 1: Chemical constituents present in Lemon.

S.NO	Constituents
1	Alkaloids
2	Flavonoids
3	Polyphenols
4	Essential Oils
5	Tannins
6	Water Soluble Vitamins
7	Glycosides

II. Tea Powder:

Astonishingly, for hundreds of years tea makers have produced drinkable teas using principles of wilting and oxidation with no knowledge of the substratal chemistry. From what we know today, the most ponderous compounds in fresh tea leaves incumbent for producing teas with covetable appearance, aroma, flavour, and taste are: polyphenols, amino acids, enzymes, pigments, carbohydrates, methylxanthines, minerals and many volatile flavour and aromatic compounds. These components undergo tempering during tea processing to produce what we'll call a 'finished' or 'made' tea – one that has been prepared and is ready for packaging or steeping.[17] Let's take a look at each of these compounds beginning with the most abundant, polyphenols.

A. Polyphenols

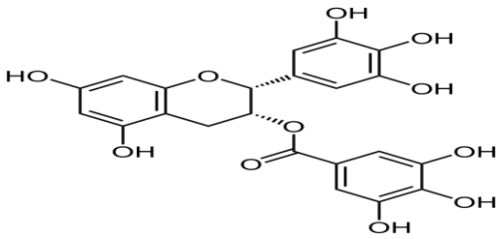

Figure 3: Epigallocatechin gallate

In pervade tea; polyphenols are largely fettered for astringency. The term polyphenol simply referred to a sorting of compounds unruffled of many phenolic groups, hence the name poly-phenol. These compounds are plant metabolites produced as a defense against insects and other animals and are the most abundant compounds in tea comprising as much as 30-40% of both freshly plucked tea leaves and solids in tea liquor.[18] They are educed from amino acids via sunlight and therefore tea grown in the shade has a smaller concentration of polyphenols and a higher concentration of amino acids. [19] The bud and first leaf have the highest concentration of polyphenols and polyphenol levels ebb in each leaf moving down the plant.[20] There is an estimation of about 30,000 polyphenolic compounds in tea, flavonoids are affably the most exigent group of polyphenols in tea and are the fount of many health claims surrounding tea, and specifically tea antioxidants. Within the flavonoid group, flavanols (also known as flavan-3-ols) are the most rampant. Flavanols are also referred to as tannins, and during oxidation are converted to theaflavins and thearubigins—the goulash censurable for the dark colour and husky flavours reputably present in black teas. The major flavanols in tea are: catechin (C), epicatechin (EC), epicatechin gallate (ECG), gallocatechin (GC), epigallocatechin (EGC), and epigallocatechin gallate (EGCG). EGCG is the hastiest of these catechins and is often the apt of studies regarding tea antioxidants. Tea flavanols are sometimes collectively adduced as catechins. Besides flavanols, tea flavonoids also include flavonols, flavones, isoflavones, and anthocyanins; all of which confer to the colour of a tea's infusion and its taste.[21]

B. Amino Acids

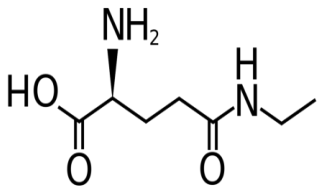

Figure 4: L-theanine

Amino acids endow tea its brothiness, or umami taste. Tea leaves embrace many amino acids, the most profuse of which is theanine. *Camellia sinensis*, a mushroom called *Boletus badius*, and an plant called *guayusa* (which is often prepared made into a tisane) are the only three natural fount of theanine found thus far in nature.[22] In the tea field, sunlight novice amino acids to polyphenols, and as such; shade grown tea subsume more amino acids than tea developed in direct sunlight. Some tea bushes are even emphatically shaded for several weeks before harvest to adorn the tea's amino acid content.[23] Theanine, more specifically L-Theanine is responsible for promoting alpha brain wave activity which promotes relaxation. L-Theanine in concert with caffeine can goose a state of "mindful alterness" in the tea drinker. In steeped tea, amino acids make up 6% of the extract solids.[24]

C. Enzymes

Polyphenol oxidase and peroxidase are the most vital enzymes in tea leaves. They are obliged for the enzymatic browning of tea leaves that takes place when the cell walls in the leaves are slivered and the polyphenols are bared to oxygen – otherwise known as oxidation.[25] These enzymes may be denatured using heat so that browning cannot occur; this is one of the first steps in green tea production and is why finished green tea leaves scraps green. The enzymes may also be revamping by simply oust them of moisture for a time which is what happens during the long drooping period in white tea production.[26]

D. Pigments

Plant dyestuffs are hampered for absorbing light for photosynthesis. Pigments also give leaves their colour. There are two major groups of pigments in fresh tea leaves: chlorophylls and carotenoids. These pigments trim during withering and oxidation and become darker. During oxidation, the green colour of tea chlorophylls is reformed to black pigments known as pheophytins. This reversal leads to the dark emergence of finished oxidized teas. Tea carotenoids are another tint group found in tea leaves and are mainly placid of carotenes which are orange and xanthophylls which are yellow and are also fettered for the colour of finished tea leaves.[27]

E. Carbohydrates

All plants hoard energy formed during photosynthesis in starches and sugars, otherwise known as carbohydrates. Plants later use this stored energy to fuel salient reactions, in tea, carbohydrates help to fuel the enzymatic reactions that take place amid oxidation and are also hampered for the creation of polyphenols in young tea leaves. Carbohydrates make up on average 11% of extract solids in steeped tea[1] and bestow to its sweetness.[28]

F. Methylxanthines

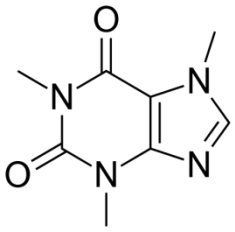

Figure 5: Caffeine

Methylxanthines in tea entail the stimulant caffeine and two similar compounds: theobromine and theophylline. The tea plant hatches these chemicals as a natural combatant towards insects and other animals. On average, methylxanthines in tea leaves make up 2% to 5% of the dry weight of the fresh leaves. Methylxanthines also tender to a bitter taste in the tea infusion. Levels of these compounds depend on the variety and cultivar of *Camellia sinensis* used, climate, age of the leaves, and the propagation method (seed vs. cutting) used on the plant.[29]

G. Minerals

28 mineral elements have been commencing in the tea flush. In comparison to other plants, tea is surpassing average amount of fluorine, manganese, arsenic, nickel, selenium, iodine, aluminium, and potassium. Tea also has a remarkably high amount of fluorine, which has been known to help anticipate tooth decay in humans, however too much fluorine can be calamitous. It is importunate to note that fluorine occurs in terrific amounts in older tea leaves. Tea minerals dissent greatly with each harvest and turn greatly during processing.[30]

H. Volatiles

The volatile substances in tea leaves are largely fettered for a tea's flavour and aroma. The aroma complex of tea is contrived up of hundreds (may be even thousands) of flavour and aroma compounds that abide in trace amounts. Many of these aromatic blends do not exist in fresh tea leaves and are derived from other substances during processing.[31] The flavour and aroma of each tea gamble on a wide variety of mishmash of these compounds, hence the name aroma complex. Compounds such as, linalool and linalool oxide are hampered for sweetness; geraniol and phenyl acetaldehyde are responsible for floral aromas; nerolidol, benzaldehyde, methyl salicylate, and phenyl ethanol are responsible for fruity flavours; and trans-2-hexenal, n-hexanal, cis-3-hexenol, and b-ionone are responsible for a

tea's fresh flavour[6]. When studying tea's aroma complex, it is sometimes broken into two parts: primary aroma (from fresh tea leaves) and secondary aroma (products of manufacture).[32] Regardless, more and more research is being done on tea volatiles and how our olfaction system works in general, so we may expect some clarity on this issue in the coming years.

Table 2: List of chemical constituents present in tea powder.

S.No	Constituents
1	Methyl Xanthines
2	Polyphenols
3	Carbohydrates
4	Enzymes
5	Pigments
6	Volatile oils
7	Minerals
8	Amino Acids

Table 3: Mechanism of action of phytochemical constituents in the treatment of diarrhoea.

S.No	Phytoconstituents	Mechanism of Actions
1	Alkaloids, Flavonoids, Tannins, Phenols, Saponins	Antidiarrhoeal; stimulation of net water absorption and reduction in electrolyte secretion
2	Terpenes	Antidiarrhoeal; altered activity of Na+ K+ ATPase or activation of chloride channels and reversal of chloride secretion

CONCLUSION

Based on literature studies and results of this investigation, one possible approach to finding novel and useful antidiarrhoeal therapeutic agents and products is to screen herbal medicines that are widely used by indigenous people or local communities to make polyherbal formulation of tea decoction with added few drops of lemon juice gives synergistic effect which helps to prevent diarrhoea and other related diseases. Correlation between antidiarrhoeal medicinal plant species and the biological activities of some of the documented plant species have been duly observed and described. While there are still gaps in the phytochemistry, mode of action, toxicity and clinical trials of the documented species, there is no doubt that some of the documented species have potential as possible sources of pharmaceutical products for the treatment of diarrhoea and related diseases.

REFERENCES

1. Wanke AC, Calderwood SB, Baron EL. Epidemiology and causes of acute diarrhea in developed countries. Cited 2012 Feb 1. Available from: gidiv.ucsf.edu/course/things/acute_diarrhea.pdf
2. Kunal G, Sanjiv K, Vijayanand W, Anti Diarrhoeal Activity of a Polyherbal Formulation in various animal models of Diarrhoea, International Research Journal of Pharmacy, 3 (8), 2012.
3. Biswall S, Proton pump inhibitors and risk for Clostridium difficile associated diarrhea, Biomedical Journal, 37:178, 2014.
4. Bethesda, MD, Symptoms and Causes of Diarrhoea, National Institute of Diabetes and Digestive and Kidney Diseases, 2016, https://www.niddk.nih.gov/health-information/digestive-diseases/diarrhea/all-content.
5. O'Toole MT, Diarrhoea, Mosby's Dictionary of Medicine, Nursing & Health Professions (9th ed.), 2013.
6. Baqui AH, Black ER, Arifeen ES, Yunus M, Zaman K, Begum N, Zinc Therapy for Diarrhoea Increased the Use of Oral Rehydration Therapy and Reduced the Use of Antibiotics in Bangladeshi Children, Journal of Health, Population, and Nutrition, 22 (4), 2004, 440–42.
7. Baltazar JC, Nadera PD, Victora GC, Evaluation of the National Control of Diarrhoeal Diseases Programme in the Philippines, Bulletin of the World Health Organization, 80, 2002, 637–43.
8. Harborne JB, Phytochemical methods, a guide to modern techniques in plants analysis, 1984, 100-117.
9. Shoba GF, Thomas M, Evaluation of anti-diarrhoeal effect of four medicinal plants on castor oil induced gastrointestinal motility in mice, Advances in Applied Science Research, 5(4), 2014, 153-156.
10. Kumar R, Sharma JR, Bairwa K, Roy KR, Kumar A, Pharmacological review on natural antidiarrhoeal agents, Der Pharma Chemica, 2(2), 2010, 66-93, http://derpharmachemica.com/archive.html.
11. Meite, S, Guessan NDJ , Bahi C, Yapi FH, Djaman JA, Guina GF, Antidiarrhoeal Activity of the Ethyl Acetate Extract of Morinda morindoides in Rats, Tropical Journal of Pharmaceutical Research, 8 (3), 2009, 201-207.
12. Wansi LS, Deumeni MRC, Kamani PLS, Sama FL, Tchoumi TML, Kuiate RJ, Antidiarrhoeal activity of aqueous and methanolic Alchornea laxiflora (Euphorbiaceae) leaves extracts in rats, Journal of Medicinal Plants Studies, 5(1), 2017, 205-211.
13. Jayshri AT, Patil VA, 3rd International Conference and Exhibition on Pharmacognosy, Phytochemistry & Natural Products, Natural Products Chemistry & Research, 2015.
14. *Gulsen, O, Roose LM, "Lemons: Diversity and Relationships with Selected Citrus Genotypes as Measured with Nuclear Genome Markers", Journal of the American Society of Horticultural Science, 126, 2001, 309–317.*
15. Spalding, William A, The orange: its culture in California, Press and Horticulturist Steam Print, 2012, p. 88.

16. Ali J, Das B, Saikia T, Anti microbial Activity of Lemon peel (Citrus Lemon) extract, International Journal of Current Pharmaceutical Research, Vol 9, Issue 4, 2017, DOI: http://dx.doi.org/10.22159/ijcpr.2017v9i4.20962.

17. *Rauf A, Uddin G, Ali J,* "Phytochemical analysis and radical scavenging profile of juices of Citrus sinensis, Citrus anrantifolia, and Citrus limonum"*, Org Med Chem Lett, 4: 5, 2004,* doi*:* 10.1186/2191-2858-4-5.

18. Harbowy, Matthew E, Douglas A, Balentine, "Tea Chemistry," Critical Reviews in Plant Sciences, 16(5), 1997, 415-480.

19. Ercisli, Sezai, Orhan E, Ozdemir O, Sengul M, Gungor N, "Seasonal Variation of Total Phenolic, Antioxidant Activity, Plant Nutritional Elements, and Fatty Acids in Tea Leaves Grown in Turkey," Pharmaceutical Biology, 46, 2008, 683–687.

20. Atlabachew M, Chandravanshi BS, Redi M. selected secondary metabolites and antioxidant activity of Khat (*Catha edulis* Forsk) chewing leaves extract, International Journal of Food Properties, 17(1), 2014, 45–64. Doi: 10.1080/10942912.2011.614367.

21. Chaturvedula VSP, Prakash I, The aroma, taste, color and bioactive constituents of tea. Journal of Medicinal Plants Research, 5(11), 2011, 2110–2124.

22. Fu L, Xu BT, Gan RY, Zhang Y, Xu XR, Xia EQ, Li HB. Total phenolic contents and antioxidant capacities of herbal and tea infusions. International Journal of Molecular Science, 12(4), 2011, 2112–2124, doi: 10.3390/ijms12042112.

23. Mendis S, Puska P, Norrving B, Global Atlas on Cardiovascular Disease Prevention and Control, 2011, 3–18.

24. Uncovering the secrets of tea – http://www.rsc.org/chemistryworld/2012/11/tea-health-benefits.

25. Zhen, Su Y, Tea: Bioactivity and Therapeutic Potential, London: Taylor & Francis, 2002.

26. Weinberg, Alan B, Bealer, Bonnie K, The World of Caffeine: The Science and Culture of the World's Most Popular Drug, Routledge, 2001, 228.

27. *Macfarlane, Alan, Macfarlane, Iris, The Empire of Tea. The Overlook Press, 2004, 32.*

28. Fukuda I, Sakane I, Yabushita Y, Kodoi R, Nishiumi S, Kakuda T, Sawamura S, Kanazawa K, Ashida H, Pigments in Green Tea Leaves (*Camellia sinensis*) Suppress Transformation of the Aryl Hydrocarbon Receptor Induced by Dioxin, Journal of Agriculture and Food Chemistry, *52* (9), 2004, 2499–2506, DOI: 10.1021/jf030786v.

29. Venipriyadharshini L, Impact of Tea on Cardiovascular Disease, International Journal of Innovative Research in Technology, Science & Engineering, Volume – 4, Issue – 2, 2018.

30. Ho, Zhu, The Chemistry of Tea, ACS Symposium Series, 754 (32), 2016, SS316–326.

31. "Tea Chemistry – Tocklai", Tocklai Tea Research Association, http://www.tocklai.org/activities/tea-chemistry.

32. Yang Z , Baldermann S, Watanabe N, Recent studies of the volatile compounds in tea, Food Research International, 2013, http://dx.doi.org/10.1016/j.foodres.2013.02.011.

33. Baldermann S, Fleischmann P, Bolten M, Watanabe N, Winter halter P, Ito Y, Centrifugal precipitation chromatography, a powerful technique for the isolation of active enzymes from tea leaves (Camellia sinensis), Journal of Chromatography A, 1216(19), 2009, 4263–4267.

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