

Honeysuckle extract review for antimicrobial protection

Dr Barbara Oliosio MRSC - The Green Chemist Consultancy, UK

Cosmetic preservation has become one of the key challenges in the industry today, triggering a great interest for alternative preservation systems that are widely antimicrobial, dermatologically and toxicologically safe and that have 'consumer friendly' INCI names, such as botanical names. Very few of these multifunctional ingredients tick all of these boxes; however, one that does is the honeysuckle extract from the *Lonicera japonica* and *Lonicera caprifolium* flowers used in Plantservative WSR by Campo Research. In this article I shall review this botanical extract combination, looking at its origin, chemistry, applications, antimicrobial performance, safety data, sustainability, parabens and formaldehyde content (or lack of).

Origin and uses

Lonicera caprifolium, also commonly called Italian honeysuckle, is a deciduous climber native to Europe. The fruit are eaten raw¹ and its flowers can be used to make tea.² In *Culpeper's Herbal*³ it is recommended to use it for asthma and to clear the skin of "morphed, freckles and sun-burning".

Lonicera japonica is a plant native to East Asia and widely used in traditional Chinese medicine (Jin Yin Hua) to treat some infectious diseases, fevers, sores and so on. On top of its use in traditional Chinese medicine it is also used in food and teas, and during the Qing dynasty it was used on the skin as a moisturiser and rejuvenator. Over 500 prescriptions containing *Lonicera japonica* are listed in the People's Republic of China Pharmacopeia. When the SARS virus hit China in 2003, this was the most popular plant used in Traditional Chinese Medicine (TCM) to treat the disease.⁴ Modern research confirms the incredible potential of *Lonicera japonica*, showing that it has antibacterial, anti-inflammatory and antiviral properties. Only a couple of years ago a team of Chinese researchers identified the *Lonicera japonica* actives capable of targeting various influenza viruses directly, suggesting it to be the first natural product



to directly target influenza A viruses.⁵ This makes the *Lonicera japonica* extract the first natural virological penicillin, with potential activity against other types of viruses as well.

Lonicera japonica is a great example of the untapped potential in plant phytochemistry when scientific research is applied to it.

Chemistry

Given *Lonicera japonica*'s interesting medicinal properties, there is a great deal of literature on this plant's phytochemistry. In fact *Lonicera japonica* has been found to contain quite a few notable substances: thirty two organic acids (none of which is para-hydroxy benzoic acid), thirty flavones (flavonoids based on 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one), thirty eight iridoids, (i.e. monoterpenes based on cyclopentanopyran), twenty eight saponins and nineteen other compounds.⁴

The ethanolic extracts were found to be rich in phenolic compounds, such as gallic acid, with interesting antioxidant as well as anti tyronase activity.⁶

The volatile components of both *Lonicera* flowers obtained via hydrodistillation were analysed and found to contain fifty seven and thirty eight compounds respectively. Farnesol and germacrene D were the molecules present at the highest concentration in both *Lonicera*s.⁷

The above composition applies to extracts obtained via traditional physical extraction methods. Interesting properties can be achieved by applying green chemistry techniques to the *Lonicera*s, where internal molecular rearrangement takes place generating new molecular structures such as the Lonicerin complex. Lonicerin is a flavonoid normally present in the plant. This complexity is key in this *Lonicera*s extract combination, making it different from other conventional extracts obtained from the same plant. The Lonicerin complex is suitable for cosmetic applications, being highly conditioning for the skin, with the additional benefit of being a broad spectrum antimicrobial agent.

The manufacturer only discloses part of the lonicerin complex molecular structure, to protect its proprietary intellectual property. The same applies to the green chemistry manufacturing method. Because of the lack of the full structure disclosure there were many speculations as to whether this extract contains formaldehyde, parabens or p-hydroxybenzoic acid, however these questions were not backed by any scientific evidence, and indeed the speculation seems misplaced and not based on any reliable experience or indeed expertise. This aspect will be covered later on in the article.

Applications, performance and regulatory status

The extract of *Lonicera japonica* and *caprifolium* based on the lonicerin complex is water soluble, pH independent, nearly colourless and with a faint odour, making it suitable for all sorts of cosmetic applications, from skin care to personal care, and it can be used as a natural microbial protection system. It is compatible with the most cosmetic ingredients (including cationic and anionic surfactants), with the exception of citral, with which it reacts giving a slight pink colour, without affecting its antimicrobial properties.

The extract does not affect surface tension and therefore it does not impact an emulsion's stability or a surfactant's viscosity. Being pH independent it can provide antimicrobial protection in a wide array of pHs and in pH shift scenarios, a rare property in alternative preservative systems. It can be used by itself as a broad spectrum preservative system at a concentration of

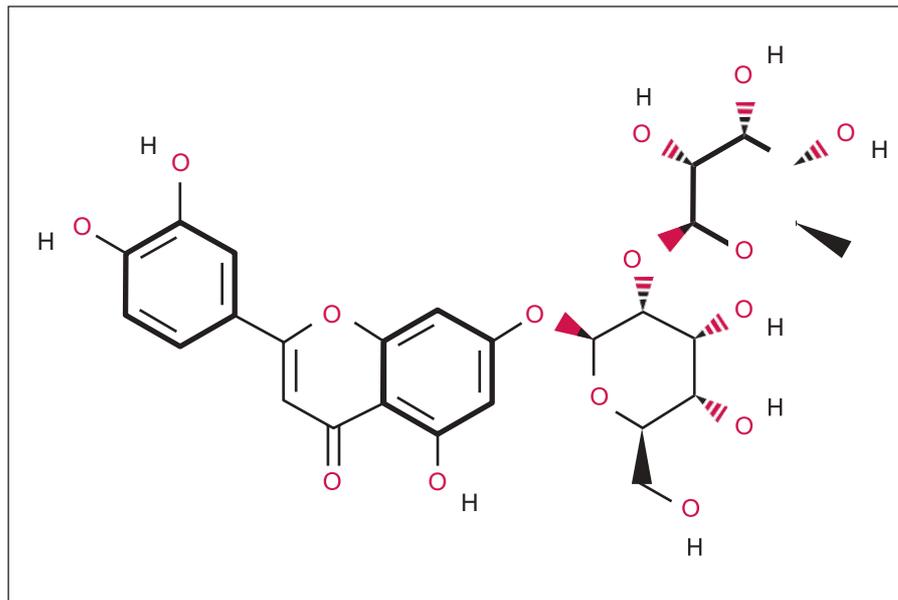


Figure 1: Multi-layered complexes of aqueous vegetal extractum of *Lonicera caprifolium* and *L. japonica* (only partial structure(s) of the multi-layered complexes of *Lonicera caprifolium* and *Lonicera japonica* shown here).

0.5%-1% depending on the formulation, without affecting product stability.

Because of its alkaline nature it is best neutralised with lactic acid, an alpha hydroxy acid already present in the skin natural moisturising factor. The extract also possesses low volatility, making it a reliable presence in formulations stored in open containers such as jars. It can also be used at a lower concentration, as a preservative booster or in combination with other natural antimicrobial protection systems. Papageorgiou et al⁸ tested the lonicerin extracts at 0.2% with 1% glyceryl caprylate, passing the EP challenge test in a couple of rinse-off formulations, but it failed in emulsion systems against *A. niger*, indicating this combination is very much formulation dependant. To boost the killing rate toward *A. niger*, the author suggests 0.1% anisic acid (providing it does not affect emulsion

stability) or 5% ethanol.

The lonicerin extract is also registered in China where it has its own SFDA IECIC index number. In addition each lonicerin has its own CTFA monograph, and it is exempt from California proposition 65 making it globally compliant.

With regards to **Japan where formaldehyde is banned, imported cosmetics undergo formaldehyde screening via a colorimetric method involving Schiff reagents. Because of the incompatibility of the lonicerins with this test, it is advisable to have the lonicerin extract tested using the manufacturer's recommended methods i.e. the AOAC 931.08 or the AOAC 964.21 used to test formaldehyde in maple syrup. If the colorimetric method screening test is used, it will give a false positive test result.**

The false positive can also be verified by a dermatological test performed on a product containing 3.5% of the lonicerin extract. The test was based on a single application with an occlusive patch test for 24 hours on a panel of 20 volunteers. The final report conclusion was 'non-irritating on intact human skin'. **If formaldehyde was present in the lonicerin extracts then this result would not have been possible being formaldehyde a known skin irritant and sensitiser. This is also confirmed by the in vitro tests performed on the raw material.**

Safety data

The lonicerin extract manufacturer commissioned an *in vitro* toxicity test using Matrex, a reconstituted skin model to evaluate irritancy potential. The test was performed using propylene glycol and morpholine as comparison controls, propylene glycol as a non-irritating one and



morpholine as a moderately irritating one. The results showed the Lonicera extract has no irritation potential, even less than propylene glycol.

The Lonicera extract was also tested for mutagenicity according to the bacterial mutation Ames test (OECD 471) and the conclusion was that it did not induce mutations. This test is used to screen for mutagenic and potential carcinogenic hazards.

Other *in vitro* tests were performed using reconstructed human epidermis, such as skin corrosivity following the OECD testing guidelines, where the conclusion was that it was a non-corrosive material. Acute eye irritation potential was also evaluated *in vitro* reconstituted human corneal epithelium and again the result was that it was non-irritant.

Parabens and formaldehyde content

A lot of opinions have been shared on the internet in the last ten years regarding the Lonicera extract, some claiming that it contains *p*-hydroxybenzoic acid, a paraben precursor, and formaldehyde.

The first claim was based on another raw material that did contain *p*-hydroxybenzoic acid from the same manufacturer - not currently used in cosmetics, but still used as an industrial grade water sanitiser (especially for Legionnaires' disease, *Legionella spp.*) for air-conditioning cooling towers. The material is also used in sanitising chicken abattoirs and poultry breeding farms from *Campylobacter jejuni*.

It is important to notice that in the articles found on the *Lonicera japonica* phytochemistry no *p*-hydroxybenzoic acid was mentioned, therefore not even the original plant seems to contain the paraben precursor.

The second claim regarding formaldehyde being present in the Lonicera extract is due to the incompatibility of the Lonicera extract with Schiff reagents. The Schiff test was originally developed in the 1800s as a reaction to detect organic aldehydes. Aliphatic aldehydes and aldose sugars react with a solution of rosoline decolourised with sulphurous acid (dye formulation and Schiff reagent). If aldehydes are present a magenta colour appears due to the formation of a chromophore compound produced by the chemical combination with the aldehyde. Therefore, if a sugar has an aldehyde group, like for example non adulterated maple syrup, and gets tested using a method where Schiff reagents or pseudo-Schiff reagents are used, a false positive for formaldehyde will appear. The same will happen if an aldehyde group is present in a fragrance compound in a



finished product. The recommended method by the manufacturer, the AOAC 964.21, avoids false positives by distilling the formaldehyde from the sample and taking a spectrophotometric reading at 415 nm of the distillate, giving a quantitative result. The AOAC 964.21, Test was developed in the 1960s to detect formaldehyde in maple syrup to avoid the false positives given by other aliphatic aldehydes or aldose sugars. While AOAC 931.08 was developed for Dairy Fresh Milk's False Positive of Formaldehyde, via Schiff Methods, Schiff Reagent and Schiff Modified Reagents

Sustainability

The Lonicera extract comes from wildy cropped plants in East Asia, therefore it is very much a sustainable, product, coming from non-intensive cultivation and with no forest destruction involved.

The extract does not have organic certification, however it complies with the standards of several green certification bodies, this includes Cosmos (Organic and Natural), Ecocert, BDIH, ICEA and Soil Association, via the relevant raw material forms.

Conclusion

The Plantservative Wsr is a successful example of green chemistry and the great potential present in every plant, waiting to be tapped into with modern green chemistry techniques. Produced from wildy cropped Japanese honeysuckle and Italian honeysuckle, without the use of any synthetic substances, it contains novel phytochemicals based on lonicerin complex with broad spectrum antimicrobial properties for cosmetic applications.

The Plantservative Wsr has an excellent dermatological profile (*in vitro* and *in vivo*) and broad antibacterial activity in several cosmetic applications, including organic certified products. Given its novel molecular structure it is not compatible with

Schiff reagents and modified Schiff reagents, therefore the manufacturer recommends particular methods need to be followed for the formaldehyde screening test i.e. AOAC 931.08 or AOAC 964.21. The full molecular structure and manufacturing method are protected by the manufacturer's intellectual property rights, however the above tests prove the authenticity of this green chemistry extract.

References

- 1 Ghirardi MP, Carli M, Del Vecchio N, et al. The importance of a taste. A comparative study on wild food plant consumptions in twenty-one local communities in Italy. *Journal of Ethnobiology and Ethnomedicine* 2007; 3:22, DOI 10.1186/1746-4269-3-22
- 2 Grieve M. A modern herbal, 1971; London, Dolver Publications
- 3 Culpeper's complete herbal, 1995; pg 273, Wordsworth Reference
- 4 Shang X, Pan H, Li M, Miao X, Ding H. Lonicera japonica Thunb: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine, *Journal of Ethnopharmacology* 2011; 138:1-21
- 5 Zhou Z, Li X, Liu J, et al. Honeysuckle-encoded atypical microRNA2911 directly targets influenza A viruses. *Cell Research* 2015; 25:39-49.
- 6 Dung NT, Bajpai VK, Rahman A. Phenolic contents, antioxidant and tyronase inhibitory activities of Lonicera Japonica Thumb, *Journal of Food Biochemistry* 2011; 35(1):148-160
- 7 Ilios DC, Radulescu V, Dtu L. Volatile constituents from the flowers of two species of Honeysuckle (Lonicera Japonica and Lonicera Caprifolium), *Farmacia* 2014; 62(1) :194-201
- 8 Papageorgiou S, Varvaresou A, Tsiaras E, Demetzos C. New alternatives to cosmetics preservation, *J. Cosmet.Sci* 2010; 61:107-123
- 9 Campo Plantservative Wsr Material Safety Data Sheet, September 2016