WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review of Historical Overview of Polyphenolic Phytoconstituents: Resveratrol and Ferulic acid.

Ambatkar Shreya*, Bangar Sonal, Naware Namrata, Kamble Tanmay, Uppar Kiran, Shirke Kshitij, Patil Mukesh, Jain Ashish.

Shri D D Vispute College of Pharmacy and Research Center, Devad, Vichumbe, New Panvel, 410206, India.

ABSTRACT:

The review mainly highlights the polyphenolic constituents that is Resveratrol and Ferulic acid. They are studied because of their various pharmacological properties such as anti-inflammatory, antioxidant, antithrombotic, anticancer, cardioprotective, and neuroprotective effects. The analytical methods are available for the qualitative and quantitative analysis of Resveratrol and Ferulic acid, but chromatographic techniques are the ones most used. Therefore, this review highlights the main analytical methods reported in the literature for determination of resveratrol and ferulic acid focusing on High Performance Liquid Chromatography (HPLC) and High-Performance Thin Liquid Chromatography (HPTLC) based methods. Also, a vast literature survey was carried out and it was concluded not enough work was done on simultaneous estimation of these drugs, therefore there is wide scope of work for the simultaneous estimation of drugs in the field of analytical method development and validation that could provide a cost effective, rapid, precise simultaneous determination of Resveratrol and Ferulic acid in combined formulation.

Key words: Analytical method, High Performance Liquid Chromatography, High Performance Thin Liquid Chromatography, Resveratrol, Ferulic Acid, Simultaneous determination.

INTRODUCTION:

Phenolic compounds (PCs) are widely dispersed phytochemicals that can be found in most plant tissues, including those of fruits and vegetables[1]. Phenolic compounds are one of the most significant and varied classes of secondary metabolites discovered in plants. Resveratrol and Ferulic acid are classified under polyphenolic phytochemicals as shown in Fig1. Resveratrol (Fig2) (trans-3,5,40 -trihydroxy stilbene) is a stilbene polyphenolic compound[2] and Ferulic acid (Fig3) (3-methoxy, 4-hydroxy cinnamic acid) is a hydroxy cinnamic acid polyphenolic compound[3]. In this review, we will look at Polyphenolic phytoconstituents like Resveratrol and Ferulic acid and the research work that has been done on it and review on the analytical methods that have been reported for the drugs.

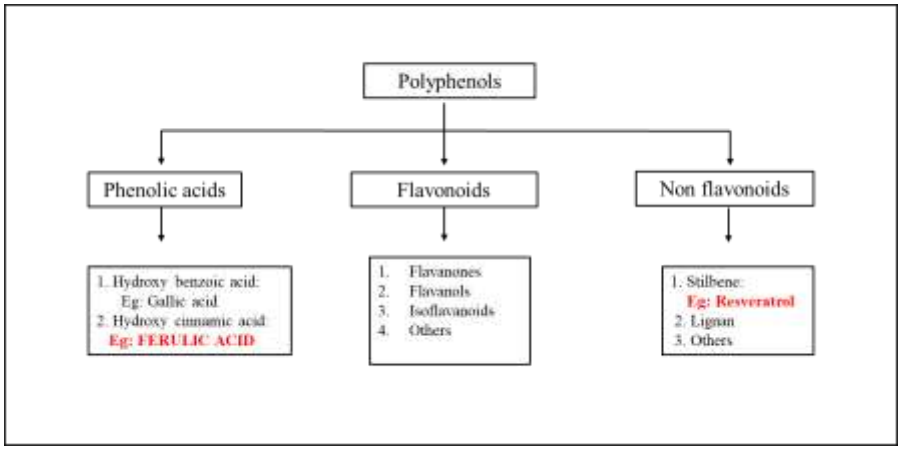

Figure 1 Classification of Polyphenols

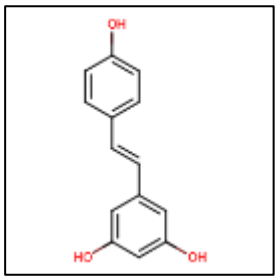

Figure 2 Chemical structure of Resveratrol[4]

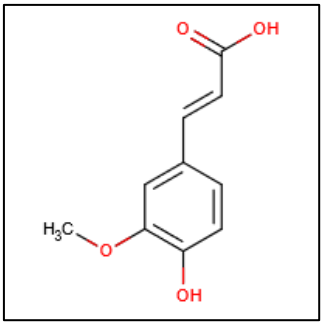

Figure 3 Chemical structure of Ferulic Acid[5]

ANALYTICAL METHODS:

Now a days, analytical method development has become the basic activity of analysis. Recent development in analytical methods has been resulted from the advancement of analytical instruments. Analytical techniques are developed and validated for active pharmaceutical ingredients (API), excipients, drug products, degradation products and related substances, residual solvents, etc[6]. Analytical method could be spectral, chromatographic, electrochemical, hyphenated, or miscellaneous. Commonly used methods for pharmaceutical analysis are detailed in the given Fig4.

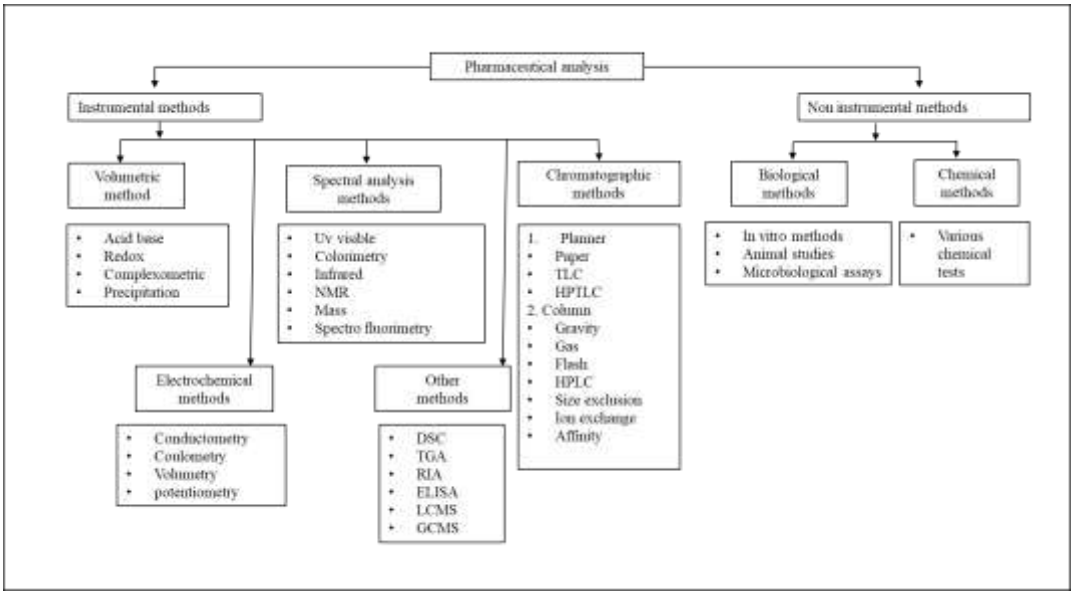

Figure 4 Classification of Analytical Methods

A. High performance liquid chromatography (HPLC): Several methods have been described for the determination and quantitation of phenolic compounds in food and plant material, most of them involved HPLC[7]. To estimate pharmaceutical and biological materials, high performance liquid chromatography (HPLC) is a crucial qualitative and quantitative approach. For the quality control of medication components, it is the most adaptable, safest, dependable, and quick chromatographic approach[8].Where High performance liquid chromatography is one of the types of chromatography used to separate, recognize, and measure each component in a mixture. Pumps are used to move a pressurised liquid solvent through a column of solid adsorbent material while carrying the sample combination within it. The slight differences in how each component

in the sample reacts with the adsorbent material results in varying flow rates for the various components and causes separation of the components as they exit the column. For manufacturing, study, and medical applications, HPLC has been used[9].

Types of HPLC generally depend on phase system used in the process:

1. Normal phase chromatography: The least popular type of HPLC nowadays, normal-phase HPLC (NP-HPLC), uses a polar stationary phase (often silica) and less polar (nonaqueous) eluting solvents, such as n-hexane and ethyl acetate (mobile phase). The analyte's capacity for polar interactions serves as the basis for the separation. In general, nonpolar chemicals in the mixture being run through the column will move through the column more quickly and be eluted faster than polar compounds, which will be adsorbed more strongly to the polar silica. Shorter retention times result from faster elution times, which are decreased by making the eluting solvent more polar[10].
2. Reversed phase chromatography: Reversed-phase The most often used HPLC mode is known as RP-HPLC, which is just NP-HPLC in reverse, with the stationary phase being more nonpolar than the eluting solvent. A nonpolar stationary phase, such as C18 silica, and a moderately polar aqueous mobile phase are typical components of RP-HPLC.
3. Size exclusion chromatography: A technique called gel permeation chromatography (GPC), also known as gel filtration chromatography (GFC) or size exclusion chromatography (SEC), involves fractionating macromolecules chromatographically based on their molecular sizes. The stationary phase consisted of cross-linked polydextran gels with different pore diameters. Such gels develop a three-dimensional network that functions as a molecular sieve when swelled in water. Low molecular weight (size), or molecules with a small hydrodynamic radius, are able to penetrate into the gel particle pores when an aqueous solution of macromolecules is allowed to move through a column containing the gel, but large molecules are excluded from the pores and pass directly through the column. This separation is known as chromatography. Because of this, the larger molecules elute first and the tiniest molecules elute last. [11]
4. Ion exchange chromatography: Ion-Exchange Ionizable molecules can be separated using chromatography (IEC) based on variations in their charge characteristics. Both mobile and stationary phases are used in this method, with the former typically being an aqueous buffer system into which the mixture to be resolved is introduced and the latter typically being an inert organic matrix that has been chemically derivatized with ionizable functional groups that carry a displaceable oppositely charged counterion. There are two conceivable IEC formats—anion- and cation-exchange—because these counterions are in an equilibrium between the mobile and stationary phases. [12]

Instrumentation: Modern HPLC includes following main elements:

1. A reservoir for solvents and a degassing device

2. Use a pump to circulate the system's eluent and sample.

3. A sample introduction device that uses injection

4. A column that separates solutes

5. Visualization device for the isolated components

6. A device to gather data and record the outcomes

Applications of HPLC in various sectors include[8]:

1. Pharmaceutical applications: pharmaceutical quality control, identification of active ingredients of dosage form.
2. Environmental applications: detection of phenolic compounds in drinking water, biomonitoring of pollutant.
3. Forensics: quantification of the drug in biological samples, determination of cocaine and metabolites in blood.
4. Flood and flavours: ensuring the quality of soft drinks and drinking water, sugar analysis in fruit juices.

B. High performance thin liquid chromatography (HPTLC): The most sophisticated type of present-day TLC is HPTLC. It makes use of HPTLC plates that contain tiny particulates with a restricted size distribution to produce homogeneous layers with a smooth surface. Smaller plates (10 10 or 10 20 centimetres) are used in HPTLC. HPTLC plates are used for industrial pharmaceutical densitometric quantitative analysis because they offer better resolution, greater detection sensitivity, and enhanced in situ quantification. [13]

Various steps involved in HPTLC are[14]:

1. Selection of chromatographic layer
2. Sample and standard preparation
3. Activation of pre coated plates
4. Application of sample and standard
5. Chromatographic development and drying

6. Detection and visualization
7. Scanning

Application of HPTLC in various sectors include[13]:

1. Pharmaceutical applications: quality control, stability testing.
2. Clinical application: metabolism studies, drug screening.
3. Forensics: investigation of poisoning, dyestuff analysis.
4. Food and feed stuff: additives (e.g., vitamins), quality control.

ANALYTICAL METHOD VALIDATION:

The idea of validation originated in the US in 1978. Over the years, the definition of validation has been expanded to encompass a variety of tasks, such as computerised systems for clinical trials, process control, or labelling, as well as analytical methods used to monitor the quality of therapeutic ingredients and drug products. Validation is best viewed as a crucial and essential component of cGMP. A high level of assurance that the product (equipment) will satisfy the requirements of the desired analytical applications is provided by the "process of establishing documented evidence" known as method validation[15].

Components of method validation

1) Accuracy

2) Precision

3) Linearity

4) Limit of detection

5) Limit of quantitation

6) Specificity

7) Range

8) Robustness

POLYPHENOLS: RESVERATROL AND FERULIC ACID

Currently, there are huge number of different combinations available in dosage forms, and their use is growing quickly. These multi component formulations offer benefits like a higher therapeutic index, numerous actions, fewer adverse effects, and quicker relief. Due to their benefits, such as being less time consuming, inexpensive, specific, and accurate, which gives results to a high degree, various instrumental techniques, such as spectrophotometric and chromatographic techniques, are used for the estimation of multiple components in formulation[16]. After detailed research work it was found that Resveratrol and Ferulic acid is available in combined formulation and the literature showed that not much work is done on simultaneous estimation of this polyphenolic phytoconstituents that is Resveratrol and Ferulic acid. The literature revealed the following methods for determining polyphenols.

According to Resurreccion. A.V.A et al, research article shows that, a RP-HPLC procedure was developed for simultaneous determination of phenolic compounds in peanuts skin extracts. Where the method includes C18 column with mobile phase 0.1% formic acid in filtered deionised water as solvent A and 0.1% formic acid in 100% acetonitrile as solvent B. The first phase involved increasing solvent B linearly from 5% to 100% over 60 min and flow rate of 1.5 ml/min where Resveratrol and Ferulic acid was determined at 318 nm and 323 nm and retention time was 80.6 mins and 42.3 mins respectively.[17]

According to Malovana. S et al, a research article on determination of polyphenolic compounds in wines by High Performance Liquid Chromatography, separation was performed on column Nova-Pak C18 150 mm × 3.9 mm i.d. from Waters, 4 mm particle diameter where The HPLC column was initially equilibrated with methanol–acetic acid–water (10:2:88, v/v) as solvent A for 10 min. The phenolic compounds were eluted with a three stages linear gradient: from 100 to 85% of A in 15 min, from 85 to 50% of A over 10 min and from 50 to 30% of A in 9 min with a total flow rate of 1.0 ml min−1. A mixture of methanol–acetic acid–water (90:2:8, v/v) was used as solvent B with detection wavelength of 280 nm[18].

Both the drugs are studied because of their various pharmacological properties. In the research article by Robinson K. et al reveals that Resveratrol (trans-3,5,40 -trihydroxy stilbene) is a stilbene polyphenolic compound that is synthesized in grapes, berries, peanuts, and plants to respond to ecological strain and pathogenic infection[2]. Due to its natural occurrence, extensive biological activity, and disease-preventive benefits on conditions including cancer, cardiovascular disease, neurological illnesses, and anti-inflammatory and antioxidant activities, resveratrol is receiving more and more attention.[19]. whereas study by Nadal. J et al shows that Ferulic acid Ferulic acid (3-methoxy, 4-hydroxy cinnamic acid) is a hydroxy cinnamic acid polyphenolic compound widely found in vegetables. Studies demonstrated that it has wide range of therapeutic action, including anti-inflammatory, antioxidant,

antithrombotic, anticancer, cardioprotective, and neuroprotective effects, as shown by earlier research also Ferulic Acid has a photoprotective impact when applied to skin[20].

Antioxidant activity: Due to the wide variety of their chemical compositions, polyphenols are thought to be even more effective than other antioxidants. Resveratrol and Ferulic acid's complex antioxidant action mechanism is primarily dependent on the inhibition of reactive oxygen species (ROS) or nitrogen synthesis, but it also involves the neutralisation ("sweeping") of free radicals[21,22].

Antimicrobial activity: Natural polyphenols like Resveratrol, suppress sebaceous lipogenesis and lessen acne vulgaris symptoms, can block the mechanistic target of rampamycin complex 1 (mTORC1), which is involved in the pathogenesis of acne, acne vulgaris is a typical skin condition [23,24,25]. Ferulic Acid is a component of anti-inflammatory medications used in Oriental Medicine and inhibits the development of both Gram-positive and negative bacteria (Escherichia coli) [26].

Anti diabetic activity: In the article by Reis et al, the endocrine disorder Increased oxidative stress and diabetes mellitus (DM), which have multifactorial origins, have been implicated as being at the core of these diseases. Resveratrol can reduce the harmful effects of Diabetes Mellitus (DM) by inhibiting the transcription of genes or inactivating proteins involved in an abnormal insulin pathway, whereas Ferulic Acid significantly decreased lipid peroxidation in adipose tissue and successfully lowered blood glucose levels, suggesting that Ferulic Acid may be helpful in lowering oxidative stress and hyperglycaemia in people with diabetes mellitus[27,28,29].

Anti carcinogenic activity: Reactive oxygen species (ROS) are thought to be a significant class of carcinogens because they have a role in the development, growth, and metastasis of neoplasia. ROS produced in the intracellular environment can directly cause changes in single-stranded or double-stranded DNA, which results in mutagenesis.

Neuroprotective activity: The neurodegenerative disorders Parkinson's disease (PA) and Alzheimer's disease (AD) are linked to chronic inflammation brought on by oxidative stress brought on by Reactive oxygen species (ROS) and reactive nitrogen species. These reactive species interfere with the function of crucial proteins, damage RNA and DNA, and cause lipid peroxidation, all of which lead to neuronal dysfunction. Resveratrol has antioxidant properties; it can reduce the production of ROS and as a result of its anti-inflammatory and protective qualities, Ferulic acid may benefit those suffering from Alzheimer's disease[19,29].

Photoprotection activity: UV light has the potential to damage DNA and cause skin cancer. Resveratrol's ability to shield the skin of SKH-1 hairless mice from numerous UVB exposure-related damages was investigated by Reagan-Shaw et al. According to the findings of this study, resveratrol may be helpful for preventing UVB-mediated damages such skin cancer because it effectively reversed UVB-mediated reactions when applied topically before UVB exposures[30]. Ferulic Acid can be used as an additive in sunscreens to improve photoprotection of the skin, hair, and fight premature and natural ageing because studies have demonstrated its efficacy in preventing skin damage from ultraviolet rays[31].

HISTORICAL OVERVIEW

Here is the brief historical evidence of HPLC estimation of Resveratrol and Ferulic acid in the Table 1

Table 1 Overview of HPLC estimation of Resveratrol and Ferulic acid

Drug	Column	Mobile phase	Flow rate	Wave length	References
Resveratrol	C18 phenomenex-Luna (4.6X250 mm)	Acetonitrile: Phosphate buffer pH 5 (28:72)	2 ml/min	305nm	[32]
	C18 – Reverse phase.	acetonitrile: water, 60:40	0.6 mL/min	307 nm	[33]
	Agilent Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm)	acetonitrile and water (27:73)	1.0 ml/min.	306.0 nm	[34]
	a Luna C18 column (5 μ 100 A Size: 100 × 4.6 mm, Phenomenex, Torrance, CA, USA)	methanol: water (40: 60)	1.0 mL/min	308 nm	[35]
	Nucleosil 100-5 C18, 250 mm × 4.0 mm, Duren, Germany)	acetonitrile–water (60:40)	0.3 mL/min	306 nm	[36]
	reverse phase C18 column (Xterra Waters) with a 5 μm particle size, 4.6 mm internal diameter, and 250 mm length.	methanol and water mixture (51: 49)	0.9 mL/min	306 nm	[37]

	YMC-Pack ODS-AM, 4.6 250 mm2 , 5 mm (YMC, Kyoto, Japan)	Acetic acid (0.5%) in a mixture of methanol and water (50:50)	1 mL/min	303 nm	[38]
Ferulic acid	C18 column	Acetonitrile: water (47:53 % v/v, pH adjusted to 3.0 with glacial acetic acid)	0.8 mL/min	322 nm	[39]
	RP C18 column (250 mm × 4.60 mm, 5 μm, 110A)	Methanol: water pH 3.0 (48:52)	1.0 mL/min	320 nm	[20]
	Enduro C 18 G (250 mm × 4.6 mm) column	methanol and water containing 1% (v/v) of acetic acid. (42:58)	1.0 ml/min	312 nm	[40]
	C18 (15cm× 4.6 mm×5 µm)	0.01 M sodium citrate containing 13% methanol with pH 5.4	1.0 ml/min	280 nm	[41]
	C18 (1o mm ×240mm × 5 µm)	0.01% acetic acid containing 28% methanol pH 3.0	1.0 ml/min	310 nm	[42]
	C18 Hypersil (200×4.6mm× 5µm)	Acetonitrile: water containing 1% of glacial acetic acid (16: 84)	0.8 ml/min	320 nm	[43]

Here is the brief historical evidence of HPTLC estimation of Resveratrol and Ferulic acid in the Table 2

Table 2 Overview of HPTLC estimation of Resveratrol and Ferulic acid

Drug	Method	References
Resveratrol	The separation was carried out on a TLC aluminium plates precoated with silica gel 60F-254 as the stationary phase, eluted with chloroform–ethyl acetate–formic acid (2.5 : 1 : 0.1) as mobile phase. Densitometric analysis of trans-resveratrol was carried out in the absorbance mode at 313 nm. This system was found to give compact spot for trans-resveratrol (Rf value of 0.40+/-0.03)	[44]
	The separation was carried out on a HPTLC mechines on to 10cm x 10cm HPTLC plates. The wavelength for detection was evaluated from complete UV spectrum of resveratrol, 313nm. Rf of resveratrol was obtained 0.34. Estimation of resveratrol in the samples was done by taking proportional comparison of area under the curve of the grape extract samples' peaks and resveratrol's peak at the Rf value of 0.34. However, all grape extract showed predominating peaks at Rf of 0.11 and was achieved in the mobile phase of chloroform-ethylactetate-formic acid (2.5 :1:0.1)	[45]
Ferulic acid	Bioactive molecules ferulic acid in *Lycopodium clavatum* was identified and estimated by the assay combined separation and quantitative estimation of the analyte on silica gel 60F254 HPTLC plates with visualization under UV and scanning at 320 nm and was achieved in the mobile phase of toluene: ethyl acetate: formaldehyde (6:3:1)	[46]

CONCLUSION

We can infer from the studies discussed in this review that Resveratrol and Ferulic acid demonstrate several biological effects that point to their effectiveness for the treatment and prevention of several pathologies. Most of the methods used to measure Resveratrol and Ferulic acid presently use HPLC, primarily because these techniques can meet the needs of selectivity and sensitivity required in most analyses. A thorough comparative study and literature review were conducted on available Resveratrol and Ferulic acid studies and research. The literature showed the available chromatographic techniques that have been reported by various research for the qualitative and quantitative determination of Resveratrol and Ferulic acid. The research or study that has been done on simultaneous estimation of these drugs is not enough, and there should be improvements in the available methods. Therefore, there is wide scope of work for the simultaneous estimation of drugs in the field of analytical method development and validation that could provide a cost effective, rapid, precise simultaneous determination of Resveratrol and Ferulic acid in combined formulation.

ACKNOWLEDGEMENT

We are thankful to our Principal SRSPM's Shri D.D. Vispute College of Pharmacy and Research Center, New Panvel-410211 for providing all necessary facility required for this research work. There was no funding received.

REFERNCES

(1) de la Rosa, L. A.; Moreno-Escamilla, J. O.; Rodrigo-García, J.; Alvarez-Parrilla, E. Phenolic Compounds. In Postharvest Physiology and Biochemistry of Fruits and Vegetables; Elsevier, 2019; pp 253–271. https://doi.org/10.1016/B978-0-12-813278-4.00012-9.

(2) Robinson, K.; Mock, C.; Liang, D. Pre-Formulation Studies of Resveratrol. Drug Dev Ind Pharm 2015, 41 (9), 1464–1469. https://doi.org/10.3109/03639045.2014.958753.

(3) Sohn, Y. T.; Oh, J. H. Characterization of Physicochemical Properties of Ferulic Acid. Arch Pharm Res 2003, 26 (12), 1002–1008. https://doi.org/10.1007/BF02994749.

(4) Resveratrol. https://go.drugbank.com/drugs/DB02709 (accessed 2023-05-12).

(5) Ferulic acid. https://go.drugbank.com/drugs/DB07767 (accessed 2023-05-12).

(6) Ravisankar, P.; Gowthami, S.; Rao, G. D. A Review on Analytical Method Development.

(7) Leucuta, S.; Vlase, L.; Gocan, S.; Radu, L.; Fodorea, C. Determination of Phenolic Compounds from Geranium Sanguineum by HPLC. Journal of Liquid Chromatography & Related Technologies 2005, 28 (19), 3109–3117. https://doi.org/10.1080/10826070500295211.

(8) Malviya, R.; Bansal, V.; Pal, O.; Sharma, P. High Performance Liquid Chromatography: A Short Review. Journal of Global Pharma Technology 2010, 2, 22–26.

(9) SHAILESH DAHIMIWAL, THORAT D.B, JAIN N.P, JADHAV V.B, PATIL P.B. A REVIEW ON HIGH PERFORMANCE LIQUID CHROMATOGRAPHY. INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH 2023, 15 (1).

(10) Sarker, S. D.; Nahar, L. Applications of High Performance Liquid Chromatography in the Analysis of Herbal Products. In Evidence-Based Validation of Herbal Medicine; Elsevier, 2015; pp 405–425. https://doi.org/10.1016/B978-0-12-800874-4.00019-2.

(11) Gellerstedt, G. Gel Permeation Chromatography. In Methods in Lignin Chemistry; Lin, S. Y., Dence, C. W., Eds.; Timell, T. E., Series Ed.; Springer Series in Wood Science; Springer Berlin Heidelberg: Berlin, Heidelberg, 1992; pp 487–497. https://doi.org/10.1007/978-3-642-74065-7_34.

(12) Cummins, P. M.; Rochfort, K. D.; O'Connor, B. F. Ion-Exchange Chromatography: Basic Principles and Application. In Protein Chromatography; Walls, D., Loughran, S. T., Eds.; Methods in Molecular Biology; Springer New York: New York, NY, 2017; Vol. 1485, pp 209–223. https://doi.org/10.1007/978-1-4939-6412-3_11.

(13) Sonia K*, Beddi Bhavya shree, Dr.K.S.Lakshmi. HPTLC Method Development and Validation: An Overview. 9 (5), 652–657.

(14) Jain, A.; Parashar, A.; Nema, R.; Narsinghani, T. High Performance Thin Layer Chromatography (HPTLC): A Modern Analytical Tool for Chemical Analysis. Current Research in Pharmaceutical Sciences 2014, 04, 8–14.

(15) Rina, R.; Baile, M.; Jain, A. A Review: Analytical Method Development and Validation. 2021, 12 (8).

(16) Pragya Nand Badyal1, Chetan Sharma1, Navdeep Kaur1, Ravi Shankar2, Abhay Pandey1 and Ravindra K. Rawal1*. Analytical Techniques in Simultaneous Estimation: An Overview. Austin Journal of Analytical and Pharmaceutical Chemistry 2015, 2 (2).

(17) Francisco, M.; Resurreccion, A. V. A. Development of a Reversed-Phase High Performance Liquid Chromatography (RP-HPLC) Procedure for the Simultaneous Determination of Phenolic Compounds in Peanut Skin Extracts. Food Chemistry 2009, 117, 356–363. https://doi.org/10.1016/j.foodchem.2009.03.110.

(18) Malovaná, S.; García Montelongo, F. J.; Pérez, J. P.; Rodríguez-Delgado, M. A. Optimisation of Sample Preparation for the Determination of Trans-Resveratrol and Other Polyphenolic Compounds in Wines by High Performance Liquid Chromatography. Analytica Chimica Acta 2001, 428 (2), 245–253. https://doi.org/10.1016/S0003-2670(00)01231-9.

(19) Koushki, M.; Amiri-Dashatan, N.; Ahmadi, N.; Abbaszadeh, H.-A.; Rezaei-Tavirani, M. Resveratrol: A Miraculous Natural Compound for Diseases Treatment. Food Sci Nutr 2018, 6 (8), 2473–2490. https://doi.org/10.1002/fsn3.855.

(20) Nadal, J.; Toledo, M.; Pupo, Y.; Padilha, J.; Farago, P.; Zanin, S. A Stability-Indicating HPLC-DAD Method for Determination of Ferulic Acid into Microparticles: Development, Validation, Forced Degradation, and Encapsulation Efficiency. Journal of Analytical Methods in Chemistry 2015, 2015, 1–10. https://doi.org/10.1155/2015/286812.

(21) Gerszon, J.; A., R.; Puchała, M. Antioxidant Properties of Resveratrol and Its Protective Effects in Neurodegenerative Diseases. Advances in Cell Biology 2014, 4. https://doi.org/10.2478/acb-2014-0006.

(22) Zduńska, K.; Dana, A.; Kolodziejczak, A.; Rotsztejn, H. Antioxidant Properties of Ferulic Acid and Its Possible Application. Skin Pharmacol Physiol 2018, 31 (6), 332–336. https://doi.org/10.1159/000491755.

(23) Kucharska, A.; Szmurło, A.; Sińska, B. Significance of Diet in Treated and Untreated Acne Vulgaris. pdia 2016, 2, 81–86. https://doi.org/10.5114/ada.2016.59146.

(24) Costa, S. C. C.; Detoni, C. B.; Branco, C. R. C.; Botura, M. B.; Branco, A. In Vitro Photoprotective Effects of Marcetia Taxifolia Ethanolic Extract and Its Potential for Sunscreen Formulations. Revista Brasileira de Farmacognosia 2015, 25 (4), 413–418. https://doi.org/10.1016/j.bjp.2015.07.013.

(25) Melnik, B. C. Acne Vulgaris: The Metabolic Syndrome of the Pilosebaceous Follicle. Clinics in Dermatology 2018, 36 (1), 29–40. https://doi.org/10.1016/j.clindermatol.2017.09.006.

(26) Edeas, M.; Khalfoun, Y.; Lazizi, Y.; Vergnes, L.; Labidalle, S.; Postaire, E.; Lindenbaum, A. [Effect of the liposolubility of free radical scavengers on the production of antigen P24 from a HIV infected monocytic cell line]. C R Seances Soc Biol Fil 1995, 189 (3), 367–373.

(27) Reis, J. S.; Veloso, C. A.; Mattos, R. T.; Purish, S.; Nogueira-Machado, J. A. [Oxidative stress: a review on metabolic signaling in type 1 diabetes]. Arq Bras Endocrinol Metabol 2008, 52 (7), 1096–1105. https://doi.org/10.1590/s0004-27302008000700005.

(28) M. Thadhani, V. Resveratrol in Management of Diabetes and Obesity: Clinical Applications, Bioavailability, and Nanotherapy. In Resveratrol - Adding Life to Years, Not Adding Years to Life; A. Badria, F., Ed.; IntechOpen, 2019. https://doi.org/10.5772/intechopen.79498.

(29) Paiva, L.; Goldbeck, R.; dos Santos, W.; Santos; Squina, F. Ferulic Acid and Derivatives: Molecules with Potential Application in the Pharmaceutical Field. Brazilian Journal of Pharmaceutical Science 2013, 49, 395–411.

(30) Reagan-Shaw, S.; Afaq, F.; Aziz, M. H.; Ahmad, N. Modulations of Critical Cell Cycle Regulatory Events during Chemoprevention of Ultraviolet B-Mediated Responses by Resveratrol in SKH-1 Hairless Mouse Skin. Oncogene 2004, 23 (30), 5151–5160. https://doi.org/10.1038/sj.onc.1207666.

(31) Saija, A.; Tomaino, A.; Trombetta, D.; De Pasquale, A.; Uccella, N.; Barbuzzi, T.; Paolino, D.; Bonina, F. In Vitro and in Vivo Evaluation of Caffeic and Ferulic Acids as Topical Photoprotective Agents. Int J Pharm 2000, 199 (1), 39–47. https://doi.org/10.1016/s0378-5173(00)00358-6.

(32) Rani, N. S.; Reddy, K. N. K.; Kumar, B. P. Spectrometric and RP-HPLC Method for the Determination of Trans- Resveratrol in Vegetarian Formulation. 2017.

(33) Al-Jumaily, E. F.; Shafiq, Z. A.; Al-Bayati, R. I. Synthesis of New Derivatives of Resveratrol and to Explore Its Potential Health Benefits. Chem Sci Trans 2012, 2 (1), 329–335. https://doi.org/10.7598/cst2013.260.

(34) Li, J.; Miao, X.; Chen, T.; Ouyang, D.; Zheng, Y. Preparation and Characterization of Pelletized Solid Dispersion of Resveratrol with Mesoporous Silica Microparticles to Improve Dissolution by Fluid-Bed Coating Techniques. Asian Journal of Pharmaceutical Sciences 2016, 11 (4), 528–535. https://doi.org/10.1016/j.ajps.2015.10.030.

(35) Pentek, T.; Newenhouse, E.; O'Brien, B.; Chauhan, A. Development of a Topical Resveratrol Formulation for Commercial Applications Using Dendrimer Nanotechnology. Molecules 2017, 22 (1), 137. https://doi.org/10.3390/molecules22010137.

(36) Cho, A. R.; Chun, Y. G.; Kim, B. K.; Park, D. J. Preparation of Chitosan-TPP Microspheres as Resveratrol Carriers: Resveratrol-Loaded Microspheres…. Journal of Food Science 2014, 79 (4), E568–E576. https://doi.org/10.1111/1750-3841.12395.

(37) da Rocha Lindner, G.; Khalil, N. M.; Mainardes, R. M. Resveratrol-Loaded Polymeric Nanoparticles: Validation of an HPLC-PDA Method to Determine the Drug Entrapment and Evaluation of Its Antioxidant Activity. ScientificWorldJournal 2013, 2013, 506083. https://doi.org/10.1155/2013/506083.

(38) Bolko, K.; Zvonar, A.; Gašperlin, M. Mixed Lipid Phase SMEDDS as an Innovative Approach to Enhance Resveratrol Solubility. Drug Dev Ind Pharm 2014, 40 (1), 102–109. https://doi.org/10.3109/03639045.2012.749888.

(39) Saini, S.; Sharma, T.; Patel, A.; Kaur, R.; Tripathi, S. K.; Katare, O. P.; Singh, B. QbD-Steered Development and Validation of an RP-HPLC Method for Quantification of Ferulic Acid: Rational Application of Chemometric Tools. Journal of Chromatography B 2020, 1155, 122300. https://doi.org/10.1016/j.jchromb.2020.122300.

(40) Musfiroh, I.; Indriyati, W.; Abadi, M. L. N.; Muchtaridi, M. ANALYSIS OF FERULIC ACID IN ARABICA COFFEE BEAN (COFFEA ARABICA L.) USING SOLID PHASE EXTRACTION–HIGH PERFORMANCE LIQUID CHROMATOGRAPHY. International Journal of Applied Pharmaceutics 2019, 151–155. https://doi.org/10.22159/ijap.2019v11i5.32077.

(41) Zupfer, J.M. (Department of Food Science and Nutrition.); Churchill, K.E.; Rasmusson, D.C.; Fulcher, R.G. Variation in Ferulic Acid Concentration among Diverse Barley Cultivars Measured by HPLC and Microspectrophotometry. Journal of agricultural and food chemistry (USA) 46 (4), 1350–1354.

(42) Kroon, P.A.; Faulds, C.B.; Ryden, P.; Robertson, J.A.; et al. Release of Covalently Bound Ferulic Acid from Fiber in the Human Colon.

(43) Li, Y.; Bi, K. HPLC Determination of Ferulic Acid in Rat Plasma after Oral Administration of Rhizoma Chuanxiong and Its Compound Preparation. Biomed. Chromatogr. 2003, 17 (8), 543–546. https://doi.org/10.1002/bmc.274.

(44) Babu, S. K.; Kumar, K. V.; Subbaraju, G. V. Estimation of Trans-Resveratrol in Herbal Extracts and Dosage Forms by High-Performance Thin-Layer Chromatography. Chem. Pharm. Bull. 2005, 53 (6), 691–693. https://doi.org/10.1248/cpb.53.691.

(45) Malele R.S1; , M.C. Zvikomborero. Estimation of Trans-Resveratrol in Grape Berry Skin Extract by High Performance Thin-Layer Chromatoghapy (HPTLC). International Journal of Research in Health Sciences 2014, 2 (1), 213–223.

(46) Srivastava, S.; Singh, A. P.; Singh Rawat, A. K. A HPTLC Method for the Identification of Ferulic Acid from Lycopodium Clavatum. Asian Pacific Journal of Tropical Biomedicine 2012, 2 (1), S12–S14. https://doi.org/10.1016/S2221-1691(12)60121-X.