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Metabolic profiling of bioactive compounds from different medicinal plants: An overview

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Abstract
Metabolomics has become an important tool in many research areas like drug discovery, diseases and nutrition, plant physiology, food quality and authenticity assessment, biomarker discovery, environmental and biological-stress studies, functional genomics, integrative systems biology, etc. It can be targeted or non-targeted. Metabolomics has been used as a vast tool for the investigation and quality measurement and assessment of natural products derived from plant and its parts. However, metabolite profiling in crude extracts is not an easy work as natural materials show a very diverse form of structure. It makes use of various analytical techniques like LC-QTOF-MS, GC-QTOF-MS, UPLC-QTOFMS, LC-ESI-QTOF/MS. In the present review, an attempt has been done to enlist metabolic profiling of 50 medicinal plants, along with their part, solvent used and number of bioactive compounds identified. Its various uses have also been discussed.

Keywords: Medicinal plants, metabolomics, metabolite profiling, analytical techniques, LC-QTOF-MS

Introduction
Metabolomic is the comprehensive analysis of all the metabolites under given set of conditions in an organism (Fiehn, 2002) [1]. According to the Massachusetts Institute of Technology (MIT) Technology Review 2005 (MIT Technology Review, 2005) [2] metabolomics is known to be one of the 10 leading breakthrough technologies. Metabolomic studies is divided into two groups viz. Targeted and non-targeted approach depending how metabolite identification is executed during data processing. In targeted approach preknown or predetermined rather specific metabolites are targeted; it is non-random approach while in non-targeted approach all metabolites are identified irrespective of its specific group; it is random approach. Each has its advantage and disadvantage viz. in targeted approach one is biased because in an unknown sample you are searching for a specific group of compounds like lipids or alkaloids giving no chance for new compounds identification while the non targeted approach may lead to *de novo* discovery of new targets or new compounds.

Some of the analytical techniques that are used in metabolomics are liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) and gas chromatography coupled to quadrupole time-of-flight mass spectrometry (GC-QTOF-MS), ultra-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry (UPLC-QTOFMS), liquid chromatography coupled with electrospray-ionization quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF/MS), etc.

Metabolomics can be accurately used to assess the quality of natural medicine or natural product derived medicine. In fact, the technique can be used for quality control and standardization of natural extracts or herbal medicine (Lee *et al*., 2017) [3]. There are 100s of plant products or plant derived medicines which are used therapeutically and use of green medicine is increasing rapidly. So it is very essential to correctly identify the plant products and maintain its identify and quality; thus this method becomes very important which can correctly identify the metabolites present in the sample. It will also aid in understanding the underlying mechanism of action. Medicinal plants belonging to same genus but different species is quite difficult to identify and are prone for mis identification and sometime drugs derived from them can be inappropriate which may decrease its therapeutic efficacy. Such difficulties can be overcome by UPLC-Q-TOF-MS technique.

Some examples of other applications are analysis and identification of secondary metabolites and their quantification in medicinal plants, to identify tissue specific metabolite content, metabolite identification in complex biological samples, to establish quality parameters and standardization, to distinguish closely related medicinal plants species, to discover novel bioactive compounds in plants, for food quality and authenticity assessment, to determine the functional significance of plant metabolites, for biomarker studies in diagnostics and drug research, for identification of plant diseases, etc.

Analyzing crude natural extracts is quite challenging because of its chemo diversity (Schwab, 2003) [4]. There are two types of metabolites in plants viz. primary and secondary or essential and non-essential; the former refers to carbohydrates, lipids, amino acids which are essential and necessary for growth and development of plants while the later include compounds like alkaloids, polyphenols, flavonoids, terpenes, saponins etc which are non-essential but necessary for defense, signaling, etc i.e. for survival in a given environment (Wolfender, *et al*., 2014) [5]. The secondary metabolites give rise to many drug molecules or lead compounds for new drugs. Metabolites are small molecules with molecular weights of <1000 Da.

Researchers used metabolic profiling for analyzing bioactive compounds from various plants and plant parts. For eg. metabolite profiling of bioactive compounds from *Bidens pilosa* was attempted by Chiang *et al*., (2004) [6]. Metabolites profiling of secondary metabolites of *Arabidopsis arabika* was done by D'Auria and Gershenzon, (2005) [7]. Rosenblum *et al*. (2005) [8] used 1H NMR metabolomics technique for environmental and biological-stress studies. Rainville *et al*., (2007) [9] used UPLC-TOF-MS for the structural elucidation of compounds like lipids in complex biological mixtures. Xie *et al*., (2009) [10] used UPLC-QTOFMS technique to identify and distinguish different tea samples like Chinese green tea, pu-erh and black tea. Gardana *et al.,* (2010) [11] analyzed steviol and its glycoside from *Stevia rebaudiana* leaves as a commercial sweetener. Zhao *et al*. (2013) [12] employed UPLC-QTOFMS for pharmacokinetic investigations of 2,3,5,4-tetrahydroxystilbene-2-O-β-D-glucoside (from *Polygoni multiflori*) in rats and reported the identification of three metabolites with the help of rapid resolution LC-MS(n). Metabolite profiling of polyphenols from *Vaccinium* berries was attempted by Prencipe *et al*., 2014 [13]. Zhang *et al*., (2018) [14] used headspace gas chromatography-mass spectrometry (HSGC-MS) and ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-QTOF/MS) to differentiate five cultivars of *Chrysanthemum morifolium.* 14 volatile and 7 nonvolatile marker compounds were identified. These methods are successfully utilized to visualize the difference in closely related medicinal plants species. Singh *et al*., (2014) [15] used HPLC-DAD/ESI-QTOF-MS/MS and UPLC-QTRAP-MS methods for identification, characterization and quantification of bioactive compounds in leaf, stem, root and fruit of *Berberis petiolaris*. Chen, *et al*. (2015) [16] investigated the antihyperlipidemic activity of rhubarb extract in high-fat diet-induced hyperlipidemic rats. UPLC-QTOF-HDMS-based urinary metabolomic profiling was used to identify 29 metabolites which were altered in hyperlipidemic rats compared to control groups. Taamalli *et al*. (2015) [17] used RP-UHPLC (reversed phase-ultra performance liquid chromatography) equipped with ESI-QTOF-MS (electrospray ionization quadrupole time-of-flight MS) for the metabolite profiling of two different Lamiaceae medicinal plants and reported the identification of 85 metabolites, including organic acids and derivatives, nucleosides, amino acids, amino acids derivatives and phenolic compound. Woldegiorgis *et al*. (2015) [18] reported the use of LC/MS/MS equipped with a QTOF mass analyzer for the comparative metabolite profiling of seven edible mushroom varieties including *P. ostreatus, A. campestris, L. edodes, L. sulphureus, T. microcarpus T. clypeatus, T. letestui* and identified biomarkers relevant to *L. sulphurous*. Song *et al*., (2016) [19] used UPLC/ESI-QTOF-MS technique to identify metabolites in bile sample of rats orally administrated with imperator in and their possible metabolic pathways were proposed. The detailed mechanism of imperator in metabolism could be studied. Wang *et al*., (2017) [20] studied metabolic content of four *Panax* species viz. *Panax ginseng, Panax notoginseng, Panax quinquefolium* and *Panax japlcus*. The genus was same but species were different and it was quite difficult to distinguish them. They have many similar chemical compounds however, the technique was successfully used to find specific marker for each species. This is a new and novel strategy to find specific biomarkers and can be applied to other medicinal plants. Sermukhamedova *et al*., (2017) [21] used HPLC quadrupole time-of-flight (Q-TOF) MS method for standardization and identification of secondary metabolites in *Leonurus turkestanicus* aerial parts.

Park *et al*., (2017) [22] used LC-QTOF-MS technique to identify and characterize the chemical profiles of the aerial parts and roots of *I. dentate*. They found 30 compounds and most of them were sesquiterpenes and flavonoids but their content was different in different parts once again confirming that the bioactive compounds of same plant but different parts are different and hence their therapeutic efficacy. Olalere *et al*., (2018) [23] used LC-MS-QTOF and ICP-MS techniques to determine phenolic composition in oleoresin extract of black and white *Piper nigrum* extracts. They could identify 17 and 20 phenolic compounds in black and white pepper extracts respectively. Martínez-Ávila *et al*., (2018) [24] used UPLC-ESI-QTOF-MS technique to establish quality parameters in *Cassia fistula* leaves. The method was used to identify many active compounds including flavonoids, phenolic acids and lignan. Jaiswal *et al*., (2018) [25] compared the tissue specific metabolite content of two species of *Achyranthes* roots by use of UHPLC-QTOFMS and concluded that cortex and the medullary ray tissues of both species possess identical constituents like steroids and saponins and thus can be used as qualitative substitutes for each other. Such studies will be useful in herbal medicine and will reduce the burden on endangered medicinal plants. Ghosh *et al.,* (2018) [26] evaluated the phytochemical constituents of *Aegialitis rotundifolia* leaves using LC-Q-TOF-MS analysis and detected 25 phytoconstituents mostly belonging to flavonoids and alkaloids.

For characterization, quality assurance and evaluation of *O. indicum* samples, LC coupled with electrospray ionization-qTOF-mass spectrometry (ESI-qTOF-MS) was performed for identification of chemical constituents of *O. indicum* (Peng *et al*., 2019) [27]. This method can be used as a reference tool for efficient separation and identification of the components in other plants of the same genus. *P. decumanum* is a medicinal fern which is popularly used for dermatological disorders, inflammation and cancer. Hence it is essential to identify its marker compounds for correct identification of the plant and its other beneficial medicinal properties. High-Performance Liquid Chromatography by Ultraviolet-Visible

and Quadrupole Time-of-Flight Tandem Mass Spectrometry (HPLC–UV–VIS–QTOF–MS/MS) technique was used for identification of chemical compounds of *P. decumanum* and tentatively identified 122 compounds which are marker compounds of this medicinal fern (Martín-Pozo *et al*., 2019) [28].

Ismail *et al*., (2019) [29] used Liquid chromatography coupled to quadrupole time of flight mass spectrometry (LC-MS/QTOF) technique to identify phytochemicals in *Adansonia digitata* fruit pulp. They identified 46 compounds which included triterpenoids, steroids, glycosides, proanthocyanidins, phenolic acids, flavonols and saponins. The secondary metabolites of the different extracts of *C. retusa* stem bark, fruits, and flowers were established by LC-MS/MS. For targeted quantification of phenols they used LCQQQMS/MS (the liquid chromatography-triple quadrupole mass spectrometry/mass spectrometry) technique and LC-QTOF MS/MS (liquid chromatography quadrupole time-of-flight mass spectrometry/mass spectrometry) technique was used for phytochemical profiling of the samples (Sinan *et al*., 2020) [30]. They identified different bioactive compounds in different concentration in different parts which were directly correlated with different antioxidant activities.

The high antioxidant capacity of *Humulus lupulus* L. and *Juniperus communis* is attributed to the presence of their rich polyphenolic content. Tang *et al*. (2020) [31] used liquid chromatography coupled with electrospray-ionization quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF/MS) technique to characterize their polyphenolic content. They identified 148 different phenolic compounds which included phenolic acids like hydroxybenzoic acids, hydroxycinnamic acids and hydroxyphenylpropanoic acids and flavonoids like anthocyanins, flavones, flavonols, and isoflavonoids. Oszmiański *et al*., (2020) [32] identified and evaluated the phenolic and iridoids compounds in roots and leaf extracts of *Dipsacus fullonum* using UPLC-PDA-MS/MS technique. The roots and leaves contained five iridoid compounds (loganic acid, loganin, sweroside, cantleyoside, and sylvestroside III); leaves had seven phenolic acids and three flavones while roots had seven phenolic acids. The leaves contained more iridoids and phenolic compounds than the roots. Thus with the help of UPLC-PDA-MS/MS technique they could identify and quantify the chemical profile of roots and leaves of *Dipsacus fullonum*.

Different researchers used LC-QTOF-MS technique in different plants and identified a number of compounds. The parts of the plants used and solvent used for extract preparation was also different. The entire process from plant powder extraction to biomolecules identification is summarized in Figure 1.

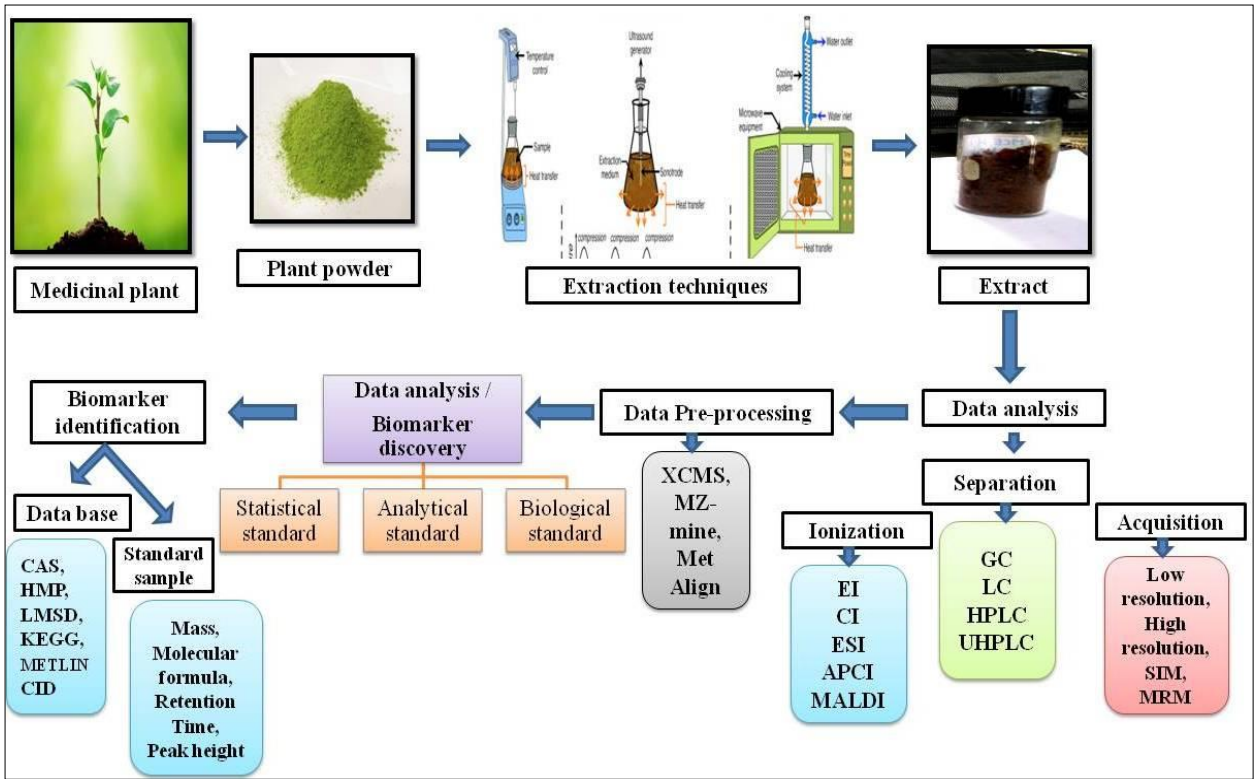

Fig 1: Schematic presentation of entire process from plant powder extraction to biomolecules identification

In the present review, 50 plants have been listed. The 50 plants belonged to 35 different families; in which 6 plants belonged to Asteraceae family, 3 plants belonged to Fabaceae family, 3 plants belonged to Lamiaceae /Labiatae family, 3 plants belonged to Araliaceae family, 2 plants belonged to Urticaceae family, 2 plants belonged to Lecythidaceae family, 2 plants belonged to Phyllanthaceae family, 2 plants belonged to Piperaceae family and 2 plants belonged to Menispermaceae family. List of fifty medicinal plants, their parts, solvent used and number of chemical compounds found in them are given in Table 1.

Table 1: List of medicinal plants, their family, parts, solvents used for extraction and number of chemical compounds present in LC-QTOF-MS technique.

S. No.	Botanical name of plants (Family)	Plant parts	Solvent	Chemical compounds	References
1	*Achyranthes bidentata* Blume. *Achyranthes aspera* L. (Amaranthaceae)	synergistic activity of root	Methanol	26	Jaiswal *et al*., 2018 [25]
2	*Adansonia digitata* L. (Bombaceae)	fruit pulp	80% Acetone	46	Ismail *et al*., 2019 [29]
3	*Aegialitis rotundifolia* Roxb. (Plumbaginaceae)	leaf	Ethanol	25	Ghosh *et al*., 2018 [26]
4	*Anoectochilus roxburghii* Wall. (Orchidaceae)	whole plant	80% ethenol	21	Xu *et al*., 2017 [33]
5	*Artemisia annua* L. (Artemisia)	Aerial parts	80% ethanol	11	Fu *et al*., 2020 [34]
6	*Asparagus officinalis* L. (*Asparagaceae*)	stalk (aerial parts)	Methanol	31	Creydt *et al*., 2018 [35]
7	*Berberis petiolaris* Wall. (Berberidaceae)	All parts (fruit, leaf, root, stem)	Ethanol	41	Singh *et al*., 2014 [15]
8	*Caesalpinia spinosa* L. *Caesalpinia decapetala* Roth. (Caesalpinaceae)	leaf	75% Ethanol	13 8	Gallego *et al*., 2016 [36]
9	*Cajanus cajan* L. (Fabaceae)	seed	Methanol	37	Tekale *et al*., 2016 [37]
10	*Canarium pimela* K.D. Koenig, Burseraceae	leaf	Ethanol	16	Wu *et al*., 2017
11	*Cassia fistula* L. (*Fabaceae*)	leaf	Aqueous	12	Martínez-Ávila *et al*., 2018 [24]
12	*Catharanthus roseus* L. (Apocynaceae)	leaf	Methyl jasmonate	34	Liu *et al*., 2017 [39]
13	*Cecropia obtusifolia* Loefl. *Cecropia peltata* L. *Cecropia insignis* L. *Cecropia hisspidisima* Berg. (Urticaceae)	Synergistic activity of leaves	70% Ethanol	47	Rivera-Mondragón *et al*., 2019 [40]
14	*Cecropia pachystachya* Trécul. (Urticaceae)	leaf	Aqueous	18	Ortmann *et al*., 2017 [41]
15	*Chrysanthemum morifolium* Ramat.(Asteraceae)	flower	50% Methanol	21	Zhang *et al*., 2018 [14]
16	*Chydenanthus excelsus* (Blume) Miers. (Lecythidaceae)	leaf	Ethyl acetate, Methanol	20 8	Rijai *et al*., 2017 [42]
17	*Cinnamomum cassia* L. (Lauraceae)	Both parts bark and twig	50% Methanol	8	Chen *et al*., 2016 [43]
18	*Couroupita guianensis* Aubl. (Lecythidaceae)	leaf	Aqueous	39	Kaneria *et al*., 2017 [44]
19	*Crotalaria retusa* L. (Fabaceae)	bark	Methanol	19	Sinan *et al*., 2020 [30]
20	*Datura stramonium* L. (Solanaceae)	leaf	Dichloromethane and Methanol (1:1)	76	Tapfuma *et al*., 2019 [45]
21	*Dipsacus fullonum L.* (Caprifoliaceae)	leaf, root	50% Methanol	5, 10	Oszmianski *et al*., 2020 [32]
22	*Humulus lupulus* L. (Cannabaceae), *Juniperus communis* L. (Cupressaceae)	hops pellet, berries	30% Ethanol	117 81	Tang *et al*., 2020 [31]
23	*Ixeris dentata* Thunb. (Asteraceae)	aerial parts	80% Methanol	30	Park *et al*., 2017 [22]
24	*Kalimeris indica* L. (Asteraceae)	whole plant	50% Ethanol	10	Zhong *et al*., 2018 [46]
25	*Lactuca sativa* L. (Asteraceae)	leaf	Methanol	76	Ismail *et al*., 2019 [29]
26	*Leonurus turkestanicus* V.I.Krecz. & Kuprian (***Lamiaceae)***	aerial parts	Ethanol	16	Sermukhamedova *et al*., 2017 [21]
27	*Lycopus lucidus* Turcz. (***Lamiaceae)***	-	60% Ethanol	37	Ren *et al*., 2017 [47]
28	*Mentha pulegium* L./*Origanum majorana* L. (Lamiaceae / Labiatae)	synergistic activity of aerial parts	Methanol	85	Taamalli *et al*., 2015 [17]
29	*Momordica charantia* L. (Cucurbitaceae)	fruit	80% Ethanol	22	Chanda *et al*., 2019 [48]
30	*Oroxylum indicum* L. (Bignoniaceae)	seed	70% Ethanol	42	Peng *et al*., 2019 [27]
31	*Panax ginseng* Meyer, *Panax notoginseng* Burk. *Panax japonicas* L. (Araliaceae)	root	70% Methanol	11, 8, 16	Xie *et al*., 2008 [49]
32	*Panax ginseng* Meyer. *Panax notoginseng* Burk. *Panax quinquefolium* L. *Panax japlcus* L. (Araliaceae)	whole plant	70% Methanol	98, 194, 74, 142	Wang *et al*., 2017 [50]
33	*Panax ginseng* Meyer. (Araliaceae)	main root, fine root, rhizome, stem, leaf	70% Methanol	76, 57, 69, 74, 44	Chen *et al*., 2019 [51]
34	*Panax quinquefolius* L. *Panax ginseng* Meyer. *Panax notoginseng* Burk. (Araliacea)	root	70% Methanol	4, 3, 3	Yuk *et al*., 2016 [52]
35	*Paullinia cupana* L. (Sapindaceae)	seed	70% Methanol	14	Da Silva *et al*., 2017 [53]

36	*Peperomia pellucida* L. (Piperaceae)	whole plant	Aqueous	4	Ahmad *et al*., 2018 [54]
37	*Phlebodium decumanum* Willd. (Polypodiaceae)	leaf,	70 % Ethanol	122	Martín-Pozo *et al*., 2019 [28]
38	*Phyllanthus emblica* L. (Phyllanthaceae)	fruit	Ethanol	8	Li *et al*., 2019 [56]
39	*Piper nigrum* L. (Piperaceae)	seed	Oleoresin	17 black 20 white pepper	Olalere *et al*., 2018 [23]
40	*Pyrus communis* L. (Rosaceae)	fruit	Methanol	18	Oikawa *et al*., 2015 [57]
41	*Rhus verniciflua* (Stokes) F. Barkley) (Anacardiaceae)	bark, lignum, leaf, fruit	80% Methanol	11, 14, 8, 1	Jang *et al*., 2018 [58]
42	*Stephania kwangsiensis* H. S. Lo (Menispermaceae)	leaf, root	Methanol	75	Shangguan *et al*., 2019 [59]
43	*Stevia rebaudiana* Bertoni. (Asteraceae)	leaf	35 % Ethanol	89	Molina-Calle *et al*., 2017 [60]
44	*Suaeda fruticose* L. (Chenopodiaceae)	leaf	Hexane	11	Saleh *et al*., 2020 [61]
45	*Terminalia catappa* L. (Combretaceae)	fruit peel	80% Methanol	53	Kaneria *et al*., 2018 [62]
46	*Tinospora cordifolia* (Willd.)(Menispermaceae)	stem	Methanol	2	Mohind *et al*., 2017 [63]
47	*Toddalia asiatica* L. (Rutaceae)	root	Methanol	59	Zhu *et al*., 2019 [64]
48	*Vernonia cinerea* L. (Asteraceae)	leaf	80 % Ethanol	9	Alara *et al*., 2018 [64]
49	*Vitis labrusca* L. (Vitaceae)	fruit	Methyl jasmonate	106	Moro *et al*., 2020 [66]
50	*Ziziphus jujube* Mill. *Ziziphus nummularia* Burm (Rhamnaceae)	whole plant	-	52 45	Khan *et al*., 2020 [67]

Conclusion

The metabolomics technique will provide a major framework for identification, quality control and quantification of bioactive molecules especially in medicinal plants. Metabolomics resources serve as a key resource for the investigation of drug discovery, plant physiology, food quality and authenticity assessment, biomarker discovery, environmental and biological-stress studies, functional genomics, integrative systems biology, etc. Metabolite profiling combines multiple analytical platforms targeted and non targeted analysis. This study represents first time a metabolomics approach that has been applied to most of the plant species, despite their importance in modern and traditional medicine.

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