International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-2, 2017, pp1496-1502
http://www.bipublication.com

**Research Article**

# Evaluation of caffeic acid derivatives ADMET as antiviral compounds

**Reza Mohammad Hasan[1],Majdedin Ghalavand[1], Mahdi Tat[1],**
**Mohammad Sadegh Hashemzadeh[1] and Ruhollah Dorostkar[1*]**

[1]Applied Virology Research Center,
Baqiyatallah University of Medical Sciences, Tehran, Iran
*Corresponding author:r.dorost@yahoo.com

**ABSTRACT**
Some herbal compounds passes antiviral activity such as caffeic acid and its derivatives. Caffeic acid derivatives are found in some medical herbs including red Sage, Echinacea, Eucalyptus, teas and coffee. Many studies have indicated that caffeic acid derivatives are susceptible to influence on influenza virus, herpes simplex virus, Rhinovirus, SAR virus, HIV, HCV and HBV, significantly. ADMET, which is a pharmaceuticalsubstance disposition description within an organism, is evaluated by computerized methods. In the article, 16 compounds of caffeic acid derivatives ADMET were investigated. The compounds data were collected from ChemSpider website. After that,ADME and toxicity were measured by Molinspiration website and ToxTree software, respectively. The resultsdemonstrated that Caffeic acid, Caffeoylmalic acid, Dactylifric acid, *p*-Coumaric acid glocuside, Coutaric acid, Ethyl Caffeate, Methyl Caffeate, Fertaric acid and Caffeic acid phenethyl esterpasses suitable ADME. Somecaffeic acid derivatives containsCaffeic acid, Caffeoylmalic acid,Chicoric acid, Caftaricacid,Coutaric acid, Ethyl Caffeate, Methyl Caffeate, Fertaric acid and Caffeic acid phenethyl ester, were categorized in toxic hazard class I. Thus, they have low toxic hazard.Consequently,caffeic acid derivatives which have low toxic hazard, suitable ADME and no violation based on Lipinski's rule of five, are capable ofapplying in drug discovery for viral diseases.
**Keywords:**Caffeic acid derivatives, Antiviral, ADME, Toxicity, Chemoinformatic

## INTRODUCTION

Many herbal compounds with antiviral activity were recognized. Some natural poly phenols such as caffeic acid derivatives belongs large family of lignin (Baillyet al., 2005).Caffeic acid derivatives are organic materials which categorized as hydroxycinnamic acidsubstances. The compounds which derived from caffeic acid, passes phenolic and acrylic functional groups. Actually, caffeic acid and its derivatives are key and intermediate materials in lignin biosynthesis in all plants (Boerjan et al, 2003). Caffeic acid derivatives are detected in fruits, vegetables, bean, honey bee propolis (Baillyet al., 2005), grains and medical plants including red Sage (*Salvia miltiorrhiza*) (Jiang *et al.*, 2005), Echinacea (*Echinacea purpurea*) (Mohammadhassanet al., 2016), Eucalyptus (*Eucalyptus globulus*) (Santos *et al*, 2011), teas (*Camellia sinensis*) and coffee (Baillyet al., 2005). By coumaroyl ester hydroxylation of quinic acid, caffeic acid is synthesized. In continuation of this process, caffeic acid ester and chlorogenic acidare produced. They are precursors of other caffeic acid derivatives (Quinde-Axellet al, 2008). Dihydroxyphenylalanine ammonia-lyase enzyme performs caffeic acid and its derivatives biotransformation into ferulic acid and its derivatives. Caffeic acid derivatives are oxidized and degraded by Caffeate 3,4-dioxygenase enzyme in present of oxygen (Olthefet al, 2001).Caffeic acid derivatives have strong inhibitory activity against viruses. Many studies have shown that Echinacea extract which caffeic acid content of them were measured by HPLC,have antiviral impacts(Mohammadhassanet al., 2016) such as deactivation of influenza virus (Vilmalanatham et al., 2005), killing herpes simplex virus (Kumar et al., 2011), sensitivity of Rhinovirus

and prevention of SARS returning (Hudson, 2012). Moreover, HIV replication is inhibited by caffeic acid derivatives (Mohammadhassan*et al*., 2016). Caffeic acid oral administration, additionally, has leaded stomach papillomas in rats (Hirose *et al*, 1998). Also caffeic acid derivatives can inhibit replication of HBV (Wang *et al*., 2009) and HCV. Antiviral activity of caffeic acid derivatives against HCV increases by enhance of Interferon alpha activity (Shen, 2013). In addition caffeic acid derivatives act as a neuraminidase of flu virus inhibitor (Xie et al., 2013).In following, it could be regarded that AMDET is abbreviation of absorption, distribution, metabolism, excretion and toxicity inpharmacokinetics and pharmacology. Indeed, ADMET is a pharmaceutical substance disposition description within an organism (Balani et al, 2005).These characteristics enable to be evaluated by computer methods. If a compound does not contain suitable ADMET characteristics, it will prone to be used as a drug (Singh, 2006). In the present article, 16 compounds ADMET of caffeic acid derivatives which have antiviral activity were studied.

## MATERIALS AND METHODS

### Compounds data collecting

Information of caffeic acid derivatives was collected from ChemSpider (http://www.chemspider.com/). ChemSpider website is a search engine for chemical compounds. It is the richest source of data based on chemical structure (Van Noorden, 2012).There are characteristics of the compounds in table 1.

### ADME evaluation

Molinspiration website (http://www.molinspiration.com/) was used to measuring of ADME (absorption, distribution, metabolismand excreti on) of thesederivatives. Molinspiration measure ADME of chemical compounds based on chemical structure (Van Noorden, 2012).

### Toxicity evaluation

Toxicity of a compound was investigated by similarities to known toxic compounds (Van Noorden, 2012). Estimation of caffeic acid derivatives toxicity was performed by ToxTree software (http://toxtree.sourceforge.net).

**Table 1.** Characteristics of Caffeic acid derivatives

| Num. | Noun | IUPAC | Chemical Formula | Ref. |
|---|---|---|---|---|
| 1 | Caffeic acid | dihydroxycinnamic acid | $C_9H_8O_4$ | Kevin *et al*, 2000 |
| 2 | Echinacoside | [(2R,3R,4R,5R,6R)-6-[2-(3,4-dihydroxyphenyl)ethoxy]-5-hydroxy-2-[[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]-4-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl](E)-3-(3,4-dihydroxyphenyl)prop-2-enoate | $C_{35}H_{46}O_{20}$ | Stoll *et al*,1950 |
| 3 | Chicoric acid | 3R-O-dicaffeoyltartaric acid | $C_{22}H_{18}O_{12}$ | Lee, 2010 |
| 4 | Caftaric acid | trans-Caffeoyl tartaric acid | $C_{13}H_{12}O_9$ | Vanzo*et al*, 2007 |
| 5 | Chlorogenic acid | 3-(3,4-Dihydroxycinnamoyl)quinic acid | $C_{16}H_{18}O_9$ | Boerjan et al, 2003 |
| 6 | Caffeoylmalic acid | (+)-(E)-caffeoyl-L-malic acid | $C_{13}H_{12}O_8$ | Budzianowski, 1990 |
| 7 | Neochlorogenic acid | 5-O-Caffeoylquinic acid | $C_{16}H_{18}O_9$ | Norattoet *al*, 2009 |
| 8 | Cynarine | 1,5-Dicaffeoylquinic acid | $C_{25}H_{24}O_{12}$ | Feifer, 2011 |
| 9 | Dactylifric acid | 3-O-Caffeoylshikimic acid | $C_{16}H_{16}O_8$ | Maier *et al*, 1964 |
| 10 | *p*-Coumaric acid glocuside | *p*-Coumaric acid 4-O-glucoside | $C_{15}H_{18}O_8$ | Strandås *et al*, 2008 |
| 11 | Coutaric acid | *trans-p*-Coumaroyltartaric acid | $C_{13}H_{12}O_8$ | Maier *et al*,2006 |
| 12 | Fertaric acid | 2-hydroxy-3-{[(2E)-3-(4-hydroxy-3methoxyphenyl)prop-2-enoyl]oxy}butandioic acid | $C_{14}H_{14}O_9$ | Vanzo*et al*, 2007 |
| 13 | Caftaric acid Conj. | 2-S-Glutathionyl caftaric acid | $C_{23}H_{27}N_3O_{15}S$ | Veronique *et al*,1986 |
| 14 | Ethyl caffeate | Ethyl (E)-3-(3,4-dihydroxyphenyl)prop-2-enoate | $C_{11}H_{12}O_4$ | Wang *et al*, 2009 |
| 15 | Methyl caffeate | methyl (E)-3-(3,4-dihydroxyphenyl)prop-2-enoate | $C_{10}H_{10}O_4$ | Gandhi *et al*, 2011 |

| | | | | |
|---|---|---|---|---|
| 16 | Caffeic acid phenethyl ester | 2-Phenylethyl (2E)-3-(3,4-dihydroxyphenyl)acrylate | $C_{17}H_{16}O_4$ | Demestre *et al*, 2008 |

## RESULTS

### ADME evaluation

ADME of 16 compounds of caffeic acid derivatives was evaluated by Molinspiration website. The data was interpreted withrespected to Lipinski's rule of five (Lipinski *et al*. 2001). The information include logP (lipophilic factor), TPSA (molecular polar surface area), number of atoms (and chemical bonds), molecular weight, number of hydrogen-bond acceptor atoms, number of hydrogen bond donor atoms, number of violationsand volume.

LogP should be under 5 with regarded to Lipinski's rule of five (Lipinski *et al*. 2001).According to the data, all caffeic acid derivatives logP were less than 5. TPSA which is less than 150is appropriate (Lipinski *et al*. 2001).

Between caffeic acid derivatives which were investigated,contain Caffeic acid, Caffeoylmalic acid, Dactylifric acid, *p*-Coumaric acid glocuside, Coutaric acid, Ethyl Caffeate, Methyl Caffeate and Caffeic acid phenethyl ester are suitable in terms of TPSA. In contrast, other compounds including Echinacoside,Chicoric acid, Caftaric acid, Chlorogenic acid, Neochlorogenic acid, Cynarine, Fertaric acid and Caftaric acid conjugated are out of suitable range. Based on Lipinski's rule of five, molecular weight should be under 500 D(Lipinski *et al*. 2001). Among of the data, Echinacoside, Cynarine and Caftaric acid conjugated don't follow the law. Molecular weights of other compounds are in suitable range.

Amount of hydrogen-bond acceptor atoms should be less than 10, according to Lipinski's rule of five (Lipinski *et al*. 2001). Between evaluated compounds, Echinacoside, Chicoric acid, Cynarine and Caftaric acid conjugated have more than 10 hydrogen-bond acceptor atoms are not adjusted with the law.Respected to Lipinski's rule of five, number of hydrogen bond donor atoms should be under 5(Lipinski *et al*. 2001).

Some caffeic acid derivatives such as Echinacoside, Chicoric acid, Neochlorogenic acid, Cynarine acid and Caftaric acid conjugated are not suitable, because they passes more than 5 hydrogen bond donor atoms. Overall, number of violations (with regarded to Lipinski's rule of five) were provided by Molinspiration website. Accordingly, Caffeic acid, Caffeoylmalic acid, Dactylifric acid, *p*-Coumaric acid glocuside, Coutaric acid, Ethyl Caffeate, Methyl Caffeate, Fertaric acid and Caffeic acid phenethyl ester have suitable ADME. Caftaric acid, Neochlorogenic acid and Chlorogenic acid own a violation due to their TSPAs which are more than 150.

Also, other caffeic derivatives including Echinacoside, Cynarine and Caftaric acid conjugated have 3 violations in cause of molecular weight mismatch, number of hydrogen-bond acceptor atoms and hydrogen bond donor atoms whit respected to the law.

### Toxicity evaluation

The results of toxicity evaluation by Tox Tree software showed that toxic hazard of Echinacoside, Cynarine, *p*-Coumaric acid glocuside and Caftaric acid conjugated are high. Also toxic hazard of Dactylifric acid, Neochlorogenic acid and Chlorogenic were evaluated intermediate. Other caffeic acid derivatives such as Caffeic acid, Caffeoylmalic acid, Chicoric acid, Caftaricacid, Coutaric acid, Ethyl Caffeate, Methyl Caffeate, Fertaric acid and Caffeic acid phenethyl ester have low toxic hazard.

Table 2. ADME and toxicity of caffeic acid derivatives data

| Num. | Noun | miLogP | TPSA | natoms | Molecular Weight | nON | nOHNH | nviolations | volume | Toxic Hazard | Toxic Hazard class |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Caffeic acid | 0.94 | 77.75 | 13 | 180.16 | 4 | 3 | 0 | 154.50 | Low | I |
| 2 | Echinacoside | -2.15 | **324.44** | 55 | **786.73** | **20** | **12** | **3** | 664.62 | **High** | **III** |
| 3 | Chicoric acid | 1.27 | **208.12** | 34 | 474.37 | **12** | **6** | **2** | 385.95 | Low | I |
| 4 | Caftaric acid | -0.61 | **161.59** | 22 | 312.23 | 9 | 5 | **1** | 251.14 | Low | I |
| 5 | Chlorogenic acid | -0.45 | **164.74** | 25 | 354.31 | 9 | 5 | **1** | 296.27 | **Intermediate** | **II** |
| 6 | Caffeoylmalic acid | 0.31 | 141.36 | 21 | 296.23 | 8 | 4 | 0 | 243.10 | Low | I |
| 7 | Neochlorogenic acid | -0.45 | **164.74** | 25 | 354.31 | 9 | **6** | **1** | 296.27 | **Intermediate** | **II** |
| 8 | Cynarine | 1.42 | **211.28** | 37 | **516.46** | **12** | **7** | **3** | 431.08 | **High** | **III** |
| Num. | Noun | miLogP | TPSA | natoms | Molecular Weight | nON | nOHNH | nviolations | volume | Toxic Hazard | Toxic Hazard class |
| 9 | Dactylifric acid | 0.31 | 144.52 | 24 | 336.3 | 8 | 5 | 0 | 282.36 | **Intermediate** | **II** |
| 10 | *p*-Coumaric acid glocuside | -0.36 | 136.68 | 23 | 326.30 | 8 | 5 | 0 | 278.6 | **High** | **III** |
| 11 | Coutaric acid | -0.12 | 141.36 | 21 | 296.23 | 8 | 4 | 0 | 243.12 | Low | I |
| 12 | Fertaric acid | -0.3 | **150.50** | 23 | 326.26 | 9 | 4 | 0 | 268.67 | Low | I |
| 13 | Caftaric acid Conj. | -5.19 | **320.4** | 42 | **617.54** | **18** | **11** | **3** | 498.19 | **High** | **III** |
| 14 | Ethyl Caffeate | 1.93 | 66.76 | 15 | 208.21 | 4 | 2 | 0 | 188.83 | Low | I |
| 15 | Methyl Caffeate | 1.56 | 66.76 | 14 | 194.19 | 4 | 2 | 0 | 172.03 | Low | I |
| 16 | Caffeic acid phenethyl ester | 3.36 | 66.76 | 21 | 284.31 | 4 | 2 | 0 | 260.48 | Low | I |

In study of toxic hazard class,Echinacoside, Cynarine, *p*-Coumaric acid glocuside and Caftaric acid conjugated were placed in toxic hazard class III. In addition,Dactylifric acid,Neochlorogenic acid and Chlorogenic were classified in toxic hazard class II. Supplementary, other caffeic acid derivatives such as Caffeic acid, Caffeoylmalic acid,Chicoric acid, Caftaricacid,Coutaric acid, Ethyl Caffeate, Methyl Caffeate, Fertaric acid and Caffeic acid phenethyl ester were classified in toxic hazard class I.

## DISCUSSION

Caffeic acid derivatives have been known as herbal secondary metabolisms(Baillyet *al*., 2005). The compounds have strong antiviral activity (Mohammadhassan*et al*., 2016). Caffeic acid derivatives are discovered in medical herb abundantly, especially red Sage (*Salvia miltiorrhiza*) (Jiang *et al*., 2005), Echinacea (*Echinacea purpurea*) (Mohammadhassan*et al*., 2016), Eucalyptus (*Eucalyptus globulus*) (Santos *et al*, 2011), teas (*Camellia sinensis*) and coffee (Baillyet *al*., 2005). For drug discovery of caffeic acid derivatives, ADMET of the compounds are essentially evaluated (Van Noorden, 2012). AMDET is abbreviation of absorption, distribution, metabolism, excretion and toxicity in pharmacology(Balani et al, 2005). The data which were obtained by Molinspiration website and ToxTree software(Van Noorden, 2012) were interpreted with regardedto Lipinski's rule of five (Lipinski *et al*. 2001). According to the results, the compounds which passes violations in their ADME indexes don't have indispensible ability of medication as a antiviral substance, like caffeic derivatives including Echinacoside, Cynarine, Caftaric acid conjugated, Caftaric acid, Neochlorogenic acid and Chlorogenic acid. Besides, caffeic acid derivatives which are placed in toxic hazard class III and their toxic hazard were estimated high are not susceptible to be used for drug discovery because of their toxicity. The other compounds which are placed in toxic hazard class II and their toxic hazard were estimated intermediate are similar to the high toxic hazard substance.

## CONCLUSION

Despite the fact that caffeic acid derivativesare herbal secondary metabolism and consumed orally, on the contrary, according to the results, which were obtained from the present research, donot have properabsorption, distribution, metabolism and excretion andthey are not appropriate to medicinal purposes. In addition, some caffeic acid derivatives have toxic hazard that is capable of poisoning. Furthermore, all compounds, which passes toxic hazard, cannot be applied as medication. Meanwhile, it is possible that caffeic acid derivatives which have low toxic hazard, proper ADME and no violation regarded to Lipinski's rule of five, are used to drug discovery for viral diseases especially viral hepatitis such as HCV, HBV, HAV and etc.

## REFERENCE


1. Bailly F., Cotelle P. (2005)" Anti-HIV Activities of Natural Antioxidant Caffeic Acid Derivatives: Toward an Antiviral Supplementation Diet". Current Medicinal Chemistry, 2005, 12, 1811-1818.
2. Balani; V.S.Devishree; G.T. Miwa; L.S. Gan; J.T. Wu; F.W. Lee (2005). "Strategy of utilizing in vitro and in vivo ADME tools for lead optimization and drug candidate selection". Curr Top Med Chem. 5 (11): 1033–8.
3. Boerjan, Wout; Ralph, John; Baucher, Marie (2003). "Ligninbiosynthesis". Annual Review of Plant Biology. 54: 519–46.
4. Budzianowski, J. (1990)."Caffeoylmalic and two pyrrole acids from Parietariaofficinalis". Phytochemistry, 1990, Volume 29, Issue 10, pages 3299–3301.
5. Demestre M, Messerli SM, Celli N,. (2008). "CAPE (caffeic acid phenethyl ester)-based propolis extract (Bio 30) suppresses the growth of human neurofibromatosis (NF) tumor xenografts in mice". Phytother Res. 23 (2): 226–30.
6. Feifer, J.(2011). "A Matter of Taste". Men's Health.
7. Gandhi, G. R., Ignacimuthu, S. Michael Gabriel Paulraj, PonnusamySasikumar, (2011). "Antihyperglycemic activity and antidiabetic effect of methylcaffeate isolated

from Solanumtorvum Swartz. fruit in streptozotocin induced diabetic rats". European Journal of Pharmacology, Volume 670, Issues 2–3, 30 November 2011, Pages 623–631.

8. Hudson J. B. (2012)." Applications of the Phytomedicine Echinacea". Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 769896, 16 pages.
9. Hirose M., Takesada Y., Tanaka S., Tamano T., Kato T., Shirai H. (1998). "Carcinogenicity of antioxidants BHA, caffeic acid, sesamol, 4-methoxyphenol and catechol at low doses, either alone or in combination, and modulation of their effects in a rat medium-term multi-organ carcinogenesis model". Carcinogenesis. 19 (1): 207–212.
10. Jiang, Ren-Wang; Lau, Kit-Man; Hon, Po-Ming; Mak, Thomas C. W.; Woo, Kam-Sang; Fung, Kwok-Pui (2005) "Chemistry and biological activities of caffeic acid derivatives from *Salvia miltiorrhiza*".Current Medicinal Chemistry, Volume 12, Number 2, January 2005, pp. 237-246(10).
11. Kevin S. Gould; Kenneth R. Markham; Richard H. Smith; Jessica J. Goris (2000)."Functional role of anthocyanins in the leaves of Quintiniaserrata A. Cunn.". Journal of Experimental Botany. 51 (347): 1107–1115.
12. Kumar K.M. and Ramaiah, S. (2011)." PHARMACOLOGICAL IMPORTANCE OF ECHINACEA PURPUREA". International Journal of Pharma and Bio Sciences.vol2, issue4, Oct-Dec 2011.p 304-314.
13. Lee J. (2010). "Caffeic acid derivatives in dried Lamiaceae and Echinacea purpurea products". Journal of Functional Foods 2, 158-162.
14. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001). "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings". Adv. Drug Deliv. Rev. 46 (1-3): 3–26.
15. Maier, VP; Metzler, DM; Huber, AF (1964). "3-O-Caffeoylshikimic acid (dactylifric acid) and its isomers, a new class of enzymic browning substrates". Biochemical and Biophysical Research Communications. 14: 124–8.
16. Mohammadhassan R., Akhavan S., Mahmoudi A., khalkhali A. ,Barzin R.(2016). "Antiviral activity of Echinacea (Echinacea purpurea)". IJBPAS, May, 2016, 5(5): 999-1005.
17. Noratto, G; Porter, W; Byrne, D; Cisneros-Zevallos, L (2009). "Identifying peach and plum polyphenols with chemopreventive potential against estrogen-independent breast cancer cells". Journal of Agricultural and Food Chemistry. 57 (12): 5219–26.
18. Olthof M. R. , Hollman P. C., Katan M. B. (2001). "Chlorogenic acid and caffeic acid are absorbed in humans". J. Nutr. 131 (1): 66–71.
19. Quinde-Axtell, Zory; Baik, Byung-Kee (2006). "Phenolic Compounds of Barley Grain and Their Implication in Food Product Discoloration". J. Agric. Food Chem. 54 (26): 9978–9984.
20. Santos, Sónia A. O.; Freire, Carmen S. R.; Domingues, M. Rosário M.; Silvestre, Armando J. D.; PascoalNeto, Carlos Pascoal (2011). "Characterization of Phenolic Components in Polar Extracts of Eucalyptus globulusLabill. Bark by High-Performance Liquid Chromatography–Mass Spectrometry". Journal of Agricultural and Food Chemistry.59 (17): 9386–93.
21. Shen H, Yamashita A, Nakakoshi M, Yokoe H, Sudo M. (2013)." Inhibitory Effects of Caffeic Acid Phenethyl Ester Derivatives on Replication of Hepatitis C Virus". plos one. December 2013.Volume 8.Issue 12.e82299.
22. Singh S.S. (2006). "Preclinical pharmacokinetics: an approach towards safer and efficacious drugs". Curr Drug Metab. 7 (2): 165–82.
23. Strandås, A. Kamal-Eldin, R. Andersson and P. Åman,. (2008)."Phenolic glucosides in bread containing flaxseed".Food Chemistry, Volume 110, Issue 4, 15 October 2008, Pages 997–999.
24. Stoll, A.; Renz, J.; Brack, A. (1950). "Isolierung und Konstitution des Echinacosids, einesGlykosidsaus den

Wurzeln von Echinacea angustifolia D. C. 6. MitteilungüberantibakterielleStoffe". Helveti ca ChimicaActa. 33 (6): 1877–1893.
25. Van Noorden, R. (2012). "Chemistry's web of data expands". Nature. 483 (7391): 524.
26. Vanzo, A; Cecotti, R; Vrhovsek, U; Torres, AM; Mattivi, F; Passamonti, S (2007). "The fate of trans-caftaric acid administered into the rat stomach". Journal of Agricultural and Food Chemistry. 55 (4): 1604–11.
27. Veronique F. Cheynier; Eugene K. Trousdale; Vernon L. Singleton; Michel J. Salgues; Renee Wylde (1986). "Characterization of 2-S-glutathionyl caftaric acid and its hydrolysis in relation to grape wines". J. Agric. Food Chem. 34 (2): 217–221.
28. Vilmalanatham S., Kang L., Amiguet V. T., Livesey J., Arnason J. T. and Hudson J.(2005)." Echinacea purpurea Aerial Parts Contain Multiple Antiviral Compounds". Pharmaceutical Biology.2005, Vol. 43, No. 9, pp. 740-745.
29. Wang, A. Choudhary, M. Iqbal; Naheed, Nadra; Abbaskhan, Ahmed; Musharraf, Syed Ghulam; Siddiqui,(2005) "Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro". Antivirus. 51 (347): 1107–1115.
30. Xie Y , Huang B , Yu K , Shi F , Liu T , Xu W. (2013). "Caffeic acid derivatives: a new type of influenza neuraminidase inhibitors". Bioorganic & Medicinal Chemistry Letters.2013, 23(12):3556-3560.