**99mTc-Luteolin: Radiolabeling, In Silico ADMET and Biological Evaluation as a Natural Tracer Tumor imaging**

Dina M. El-Sharawy\textsuperscript{a,b,c}, S. I. Khater\textsuperscript{b,d}, Essam H.M\textsuperscript{b,e}, Noheir H. Sherif\textsuperscript{f,g}, Hossam M. Hassan\textsuperscript{g,h} and Abeer H. Elmaidomy\textsuperscript{a,h}

\textsuperscript{a}Labeled Compounds Department, Hot Lab. Center, Egyptian Atomic Energy Authority (EAEA), Cairo, Egypt; \textsuperscript{b}Cyclotron Project, Nuclear Research Centre, Cairo, Egypt; \textsuperscript{c}Department of Pharmaceutics and Clinical Pharmacy, Faculty of Pharmacy, Nahda University (NUB), Beni-Suef, Egypt; \textsuperscript{d}Radioactive Isotopes and Generators Department, Hot Lab. Center, Egyptian Atomic Energy Authority (EAEA), Cairo, Egypt; \textsuperscript{e}Biotechnology Department, Nuclear Research Center, Egyptian Atomic Energy Authority (EAEA), Cairo, Egypt; \textsuperscript{f}Drug Radiation Research Department, National Center for Radiation Research and Technology Atomic Energy Authority, Egypt; \textsuperscript{g}Department of Pharmacoegnosy, Faculty of Pharmacy, Nahda University, Beni-Suef, Egypt; \textsuperscript{h}Department of Pharmacognosy, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

**ABSTRACT**

The focus of the staged work was radiolabelled 5,7,3ʹ, 4ʹ tetra-hydroxy flavone (Luteolin), isolated from Plantago lanceolata L., (F. Plantaginaceae), with \textsuperscript{99m}Tc-technetium (\textsuperscript{99m}Tc) to produce a natural tracer \textsuperscript{99m}Tc-Luteolin (\textsuperscript{99m}Tc-Lut), and to evaluate the biological distribution in silico and in vivo. Labeling was carried out by reduction reaction using SnCl\textsubscript{2}, as reducing agent giving a maximum radiochemical yield (RCY) up to 97\% at 40°C, pH4, for 30 min., with concentration of \textsuperscript{99m}Tc and Luteolin of 150 \textmu L. The tracer (\textsuperscript{99m}Tc-Lut) showed 12 h, \textit{in vitro} stability. \textit{In silico} ADMET screening of \textsuperscript{99m}Tc-Lut indicated its high bioavailability in all body organs. The bio-distribution profile indicating the highly uptake of the tracer \textsuperscript{99m}Tc-Lut, in tumor mice target/non-target ratio (T/NT) up to two-fold compared to normal mice, whereas the clearance from mice was observed via both renal and feces pathway. \textsuperscript{99m}Tc-Lut, could be valued as a probable natural radiopharmaceutical tracer for tumor appearance.

1. Introduction

Flavonoids cover a wide group of the plants secondary metabolites, defined by a diphenyl propane structure (C\textsubscript{6}-C\textsubscript{3}-C\textsubscript{6}), and were generally scattered in the plant kingdom, in fruits, vegetables and even certain beverages (López-Lázaro, 2009). Chemically, flavonoids arranged into several classes; flavones, flavanones, flavonols, isoflavones, flavanoneol, and flavan-3-ols, based on their biosynthetic origin (Kumar & Pandey, 2013).

\textit{P. lanceolata}, is a perennial acaulescent plant, and is among the widespread species growing in Turkey. Where, \textit{P. lanceolata} aerial parts have been informed to have catharses, cytotoxic, anti-inflammatory, antibacterial, diuretic, anti-gout, anti-asthamtic and wound healing potential activities (Adams et al., 2009; Fons et al., 1998; Galvez, 2003; Olouni et al., 2011; Shipochliev et al., 1981). According to literature, flavonoids were one of the most important classes’ compounds in Plantago species, specially luteolin and its glycosides (Kawashy et al., 1994).

Luteolin is a broadly distributed flavones in the plant kingdom, which is raised mainly in the form of aglycone, glycoside (O-, or C- glycoside), or methylated derivatives (Elmaidomy et al., 2019; Souleles & Laskaris, 1988). Luteolin and its glycosides derivatives, reported to have anti-inflammatory, and antioxidant activities (Cai et al., 1997; Chen et al., 2007). Several \textit{in vivo} investigations hint that luteolin had also cancer chemopreventive activity, with different mechanism (Elangooven et al., 1994; Manju & Nalini, 2007, 2005). As luteolin has a broad field of \textit{in vitro} biological activities, its bioavailability and metabolism must be studied to be significant in an \textit{in vivo} environment.

Radiopharmaceuticals are molecules that contain a radionuclide, and are used for diagnosis or therapy in clinical setting. Consequently, this radioactive drug could be utilized for the investigation and/or the healing of diseases (Rennie, 1999). The main group of these compounds was the radiotracers, which was a synthetic compound, in which one or more atoms were changed by a radionuclide. So by depending on its radioactive decay; it could be utilized to examine the chemical reactions mechanism by tracking the line that the radioisotope followed, from reactants to products (Rennie, 1999). Radiolabeling or radiotracing was thus the radioactive form of an isotopic labeling. Radioisotopes of phosphorus, carbon, hydrogen, technetium, iodine, and sulfur, have applied broadly to track the passage of the biochemical reactions. A radioactive tracer could still be handled to line the circulation of a material within a natural system as a tissue or cell (Rennie, 1999).
In this study, luteolin was isolated from *P. lanceolata*, labeled with \(^{99m}\text{Tc}\) through reduction reaction in the presence of SnCl\(_2\). *In silico* and *in vivo* tissue distribution comparative study of \(^{99m}\text{Tc}\)-Lut, in healthy and solid-tumor-bearing, male Swiss albino mice, was investigated.

2. Materials and methods

2.1. Plant materials

The plant under investigation was collected and identified. Time of collection and the detailed identification method of *P. lanceolata* aerial parts were mentioned in supplementary data (S2).

2.2. Chemicals and reagents

Details of chemicals and reagents used in this experiment were mentioned in supplementary data page (S2-3).

2.3. Apparatus

The apparatus details used in this experiment were mentioned in supplementary data page (S3).

2.4. Extraction and fractionation of the plant material

The plant under investigation was powdered, extracted and fractionation steps used in this experiment were mentioned in supplementary data page (S3-4).

2.5. Isolation and purification of compound

The major isolated compound was isolated from *P. lanceolate* and identified as luteolin using \(^1\text{H}-\) and \(^{13}\text{C}\)-NMR and physicochemical properties all the detailed experiment were mentioned in supplementary data page (S4).

2.6. *In silico* ADMET Properties of luteolin

The details for *in silico* ADMET Properties of luteolin were mentioned in supplementary data page (S5-6).

2.7. Labeling of Luteolin with \(^{99m}\text{Tc}\)

Details of labeling Luteolin with \(^{99m}\text{Tc}\) were mentioned in supplementary data page (S6).

2.8. Radiochemical Purity of \(^{99m}\text{Tc}\)- luteolin

Identification of radiochemical Purity of \(^{99m}\text{Tc}\)-Lut, in this experiment was mentioned in supplementary data page (S6).

2.9. Animal treatment

The animals used, was treated and kept in suitable environmental conditions as mentioned in supplementary data page (S7).

2.10. Animal Ethical Statement

The study was tested in compliance with rules determined by animal ethics committee of Egyptian atomic energy authority.

2.11. Induction of tumor in mice

Steps for tumor induction in mice were mentioned in supplementary data page (S7).

2.12. *In vivo* tissue distribution study of \(^{99m}\text{Tc}\)-Luteolin in mice

*In vivo* tissue distribution study of \(^{99m}\text{Tc}\)-Lut, in mice steps were mentioned in supplementary data page (S7).

2.13. Statistical analysis

Details of statistical analysis used in this experiment were mentioned in supplementary data page (S8).

3. Results and discussion

3.1. Phytochemical investigation of luteolin

Based on the chromatographic properties, physicochemical, spectral analyses of UV, \(^1\text{H},^{13}\text{C}\) NMR, beside comparison with the literature and authentic sample, data of compound 1 suggested possible 5, 7, 3', 4' tetra substituted flavone core scaffold (Ozgen et al., 2011). The \(^1\text{H}, \) and \(^{13}\text{C}\) NMR data (Table 1) suggested 6 characteristic methine resonating peaks appeared at \(\delta_H\) 6.52 (1H, s) \(\delta_C\) 102.95, \(\delta_H\) 6.12 (1H, s) \(\delta_C\) 99.51, \(\delta_H\) 6.40 (1H, s) \(\delta_C\) 94.57, \(\delta_H\) 7.23 (1H, s) \(\delta_C\) 116.48, \(\delta_H\) 6.87 (1H, d, \(J = 7.5\)) \(\delta_C\) 113.46, and \(\delta_H\) 7.23 (1H, d, \(J = 7.5\)) \(\delta_C\) 119.59. Additionally, the

| Position | \(\delta_C\) | \(\delta_H\) (J in Hz) |
|----------|-------------|----------------------|
| 2, qC    | 164.82      |                     |
| 3, CH    | 102.95      | 6.52 (s)             |
| 4, qC    | 182.07      |                     |
| 5, qC    | 161.48      |                     |
| 6, CH    | 99.51       | 6.12 (s)             |
| 7, qC    | 164.44      |                     |
| 8, CH    | 94.57       | 6.40 (s)             |
| 9, qC    | 157.73      |                     |
| 10, qC   | 103.85      |                     |
| 1', qC   | 121.83      |                     |
| 2', CH   | 116.48      | 7.23 (s)             |
| 3', qC   | 145.88      |                     |
| 4', qC   | 150.04      |                     |
| 5', CH   | 113.46      | 6.87 (s)             |
| 6', CH   | 119.59      | 7.23 (s)             |

qC = quaternary, CH = methane
3.2. In silico ADMET Properties of luteolin

In silico ADMET profiling of luteolin, utilizing PreADMET program version 2.0, indicated that, this flavones had a middle absorption to BBB (0.367582), a high absorption to HIA (79.427233), strong bounding to PPB (99.717233), moderate SP (−4.28017), middle Caco-2 (4.53973), MDCK permeability (36.5205). Also, luteolin inhibited CYP2C9, CYP2C19, and CYP3A4 and with no effect in Pgp. Toxicity screening results using PreADMET, showed mutagenicity against AMES test with a positive mode with TA100_NA, and potential rat and rodent carcinogenicity. Also, hERG inhibition was of a medium risk. The results of the in silico screening showed that luteolin theoretically was potentially high bioactive. These features were showed by its low plasma concentrations, due to its extensive cellular uptake (Singh, 2006). Tight control of the compound plasma concentrations was achieved through binding to serum albumin (Fitzpatrick & Wynalda, 1981), which lowered plasma concentrations of the unbound bioactive compound; while giving a storage system for prolonged release into the plasma. Moreover, albumin-bound compounds were more safe against oxygen-dependent degradation, resulting in prolonging their biological availability, and further extending their plasma half-life. This reply would protect target tissues from high-level uptake of compound, which might produce a toxic reaction in the cells (Fitzpatrick & Wynalda, 1981). Indeed, delayed release of this compound from plasma proteins would establish a more constant rate of cellular uptake. Besides that, the ADME properties for this compound increased its toxicity and carcinogenicity at long-term use.

3.3. Labeling of luteolin with 99mTc

99mTc was used was for labeling luteolin using SnCl2,2H2O (Spies & Pietzsch, 2007). Labeling of different anticancer drugs take an interest in last century to act as a tracer for imaging and treating cancer as 99mTc-zolmitriptan as lung cancer imaging (Rashed et al., 2016), 125I-sibutramine for brain imaging (Motealeb et al., 2011), The different parameters which change the radiochemical yield of 99mTc – Lut, were studied as follow

3.3.1. Effect of pH of the reaction

According to this study, pH found to have a great change on the labeling yield of 99mTc -Lut. Where, a maximum yield (87%) obtained at pH 4. While, pH at neutral or alkaline region found to decrease the yield to 27, 50%, respectively (Figure 2). This finding suggested that, luteolin work best in mild acidic medium.

3.3.2. Effect of reaction time

According to this study, short reaction time was poor to form the complex, leading to a low yield of 99mTc – Lut, (Figure 3) (Essa et al., 2015). On the other hand, increasing the reaction time to 30 min., showed significant increase in the radiochemical yield of 99mTc – Lut, up to 92.5%. While, further increasing of the reaction time over 30 min., has almost no effect (Figure 3).

3.3.3. Effect of temperature

This study showed that, the maximum radiochemical yield of (99mTc – Lut, (97%)) (Figure 4), was obtained at 40°C. Increasing temperature above the previous value around 50–80°C, decreased 99mTc – Lut., yield, as the rate of side reaction, increased (Amin et al., 2009).

3.3.4. Effect of 99mTc content

This study showed that, 99mTc-Lut, yield increased to 97% by increasing 99mTc concentration to 150 μL, at 40°C for 30 min (Figure 5). And quite the opposite, increasing 99mTc concentration >150 μL, decreased gradually 99mTc-Lut, yield through the colloid increasing (Ibrahim et al., 2011).

3.3.5. Effect of luteolin amount

This study showed that, at low concentration; 50μL 99mTc-Lut, yield was poor (60%), and this finding suggested insufficient ligand amount to complex with all reduced99mTc (Rashed et al., 2016).While, increasing the concentration of luteolin up to 150μL, 99mTc-Lut, yield reached to maximum value (97%), further increasing don’t affect (Figure 6 and 7).

3.3.6. Effect of reaction temperature with time

The relation between the reaction time and the yield of 99mTc-Lut, at various temperatures was studied.
Figure 2. Variety of radiochemical yield of $^{99m}$Tc-Lut., as a function of pH [150 μL Lut. +100 μL buffer at different pH+150 μL SnCl$_2$] at room temperature within 30 min.

Figure 3. Variety of radiochemical yield of $^{99m}$Tc-Lut.[150 μL Lut. +100 μL buffer pH4 + 150 μL SnCl$_2$] at RT for X min.

Figure 4. Variety of radiochemical yield of $^{99m}$Tc-Lut., [150 μL Lut. +100 μLbuffer pH4 + 150 μL SnCl$_2$] at different temperature within 30 min.

Figure 5. Variety of radiochemical yield of $^{99m}$Tc-Lut., [150 μL Lut. +100 μLbuffer pH4 + X μL SnCl$_2$] at 40 °C for 30 min.
Radiochemical yield of $^{99m}$Tc-Lut, was significantly increased from 77.5 to 93.8%, with increasing reaction time from 5 min to 30 min., extending the reaction time >30 min does not affect the radiochemical yield in room temperature. While, reaction at 40°C showed no significantly increasing in $^{99m}$Tc-Lut, yield. In case of 60 °C, the radiochemical yield was lower comparing to 40 °C, and this finding suggested side reactions (Amin et al., 2009). Consequently, the maximum yield of $^{99m}$Tc-Lut, was obtained at 40 °C for 15 min.

3.3.7. In-vitro stability of $^{99m}$Tc-Luteolin

The tracer was stable up to 12 h., at room temperature (25°C). It is significant to know the proper time for injection to reduce the development of the undesired products that arise from the radiolysis of the labeled compound as illustrated in Table 2.

| Time (h.) | Radiochemical stability (%) |
|-----------|-----------------------------|
| 1         | 97.0                        |
| 2         | 97.7                        |
| 4         | 96.5                        |
| 8         | 96.0                        |
| 12        | 95.0                        |
| 16        | 90.0                        |
| 24        | 84.5                        |

3.4. Radiochemical Purity of $^{99m}$Tc-luteolin

The radiochemical purity of $^{99m}$Tc-Lut, was determined using electrophoresis analysis. Samples investigation from the reaction mixture produced two peaks (Figure 8). One was corresponding to the free technetium, which migrated toward the anode, with 11 cm distance, while $^{99m}$Tc-Lut, at the stage of spotting, depending on their charge and ionic mobility (Ibrahim et al., 2011). It gave radiochemical yield equal to 97%.

Figure 6. Variety of radiochemical yield of $^{99m}$Tc-Lut, [X μL Lut. +100 μLbuffer pH4 + 150 μL SnCl2] at 40 °C for 30 min.

Figure 7. Variety of radiochemical yield of $^{99m}$Tc-Lut, [150 μL Lut. +100 μLbuffer at pH4 + 150 μL SnCl2] at RT within Y min.

Table 2. Stability of $^{99m}$Tc – Lut., at room temperature.

Figure 8. Electrophoresis of $^{99m}$Tc luteolin.
3.5. Biodistribution of ⁹⁹ᵐTc-Luteolin in mice

In healthy group, it was noticed that the blood uptake at 30 min. was about 14.7% decreased to 4.6% after 180 minutes, nine luteolin metabolites was spotted in mice plasma and bile by liquid chromatography-tandem mass spectrometry, where luteolin-3′-glucuronide revealed the highest systemic exposure among them (Wang et al., 2017). Luteolin was picked up in the rat plasma as two metabolites; the glucuronidate or sulfate forms of the O-methylate conjugate (Sarawek et al., 2008). Data from the present investigation indicated that ⁹⁹ᵐTc-Lut, experienced high blood to tissue perfusion after only 30 min., (Table 3). Data also showed ⁹⁹ᵐTc-Lut, continued to leak from the blood to the peripheral tissue after 180 min., and there was different tissue distribution kinetics, with more affinity of ⁹⁹ᵐTc-Lut, to stomach, GIT and liver tissues, about 25.7%, 15.7% and 16.3% respectively, at 30 min., post injection (Table 3). This uptake seemed to be stable or somewhat increased at 180 min., where absorption of flavone takes place in the digestive path while microorganisms participate in their hydrolysis (Makarova, 2011). Luteolin and its metabolites dispense in the gastro-intestine, kidney, liver, and lung; while biliary excretion influenced the elimination pathways of conjugated luteolin (Deng et al., 2017). Kinetics studies recommended two pathways in rat liver participated in the metabolic mood of luteolin, the methylation and glucuronidation which improve for each other, and the glucuronidation was the predominant one (Wang et al., 2017). Luteolin undergoes Enterohepatic recirculation (Sarawek et al., 2008). At 180 min., post injection, the activity taken by the gathered urine was about 3.6%, the urinary elimination of luteolin appeared to be not the main excretion route (Walle et al., 2001). Shimoji et al. (1998), reported an excretory recovery of unmodified luteolin in rat urine of 4%. Muscarinic acetylcholine receptors were reported to be involved in the renal effects of luteolin (Boeing et al., 2017). Excretion via feces; may be the chief route of elimination of luteolin, and its metabolites (Walle et al., 2001). In our data feces, uptake showed 2.8% after 30 min., till reaching about 8% after 180 min. Ying et al. (2008) established the RP-HPLC method, which showed that the total accumulative excretion of luteolin was 37% (11% in urine, 26% in feces and bile). In the present study, the muscle uptake was about 10.2% at 30 min., post injection and decreased to 5.5% at 180 min., (Table 3). ⁹⁹ᵐTc-Lut, showed low brain uptake, about 0.1%, throughout the 180 min.

The bio-distribution of ⁹⁹ᵐTc-Lut, tracer in solid tumor-bearing mice was investigated (Table 3). Solid tumor was induced into the right thigh muscle and the left thigh muscle was selected as control. It was found that the uptake by the tumor muscle was 10.6% at 30 min., post-injection, reaching to 9.6% at 180 min., while the uptake of the control muscle was 5.1% at 30 min., post-injection decreased to 3.8% through the 180 min. Data showed that ⁹⁹ᵐTc-Lut, tended to accumulate in tumor muscle versus healthy muscle, by a comparative increase (Table 3).

### 4. Conclusion

Luteolin was isolated from *P. lanceolata*, labeled with ⁹⁹ᵐTc through reduction reaction in the presence of SnCl₂ at 40°C (pH4) within 15 min., to obtain the labeling ⁹⁹ᵐTc-Lut, with maximum yield of 97%. The tracer ⁹⁹ᵐTc-Lut, shows 12 hr in-vivo stability. *In silico* ADMET screening of ⁹⁹ᵐTc-Lut, indicated its high bioavailability. *In vivo* tissue distribution comparative study of ⁹⁹ᵐTc-Lut, in healthy and solid-tumor-bearing, male Swiss albino mice, showed the highly uptake of tracer ⁹⁹ᵐTc-Lut, in tumor mice T/NT ratio up to twofold normal mice whereas the clearance from mice established by RP-HPLC method to proceed via both renal and feces.

| Organ and body fluids | 30 min. | 60 min. | 180 min. |
|-----------------------|---------|---------|----------|
|                       | H.      | T.      | H.       | T.       |
| Blood                 | 14.7 ± 0.9 | 12.3 ± 0.2 | 13.4 ± 2.0 | 9.5 ± 0.8 |
| Bone                  | 6.8 ± 0.5 | 4.5 ± 0.02 | 7.9 ± 0.2 | 4.6 ± 0.2 |
| Muscle                | 10.2 ± 0.6 | 5.1 ± 0.1 | 3.9 ± 0.2 | 6.5 ± 0.4 |
| Tumor                 | 10.6 ± 2  | 11.1 ± 0.8 | 5.5 ± 0.3 | 3.8 ± 0.2 |
| Stomach               | 25.7 ± 3 | 20.5 ± 0.2 | 26 ± 7 | 22 ± 2 |
| Intestine             | 15.7 ± 0.9 | 8.8 ± 1 | 17.5 ± 5 | 19.5 ± 2 |
| Liver                 | 163 ± 1 | 161 ± 1 | 193 ± 5 | 172 ± 4 |
| Spleen                | 0.6 ± 0.01 | 0.21 ± 0.01 | 0.63 ± 0.02 | 0.32 ± 0.01 |
| Kidney                | 3.9 ± 0.01 | 4.5 ± 0.02 | 3.8 ± 0.01 | 2.3 ± 0.02 |
| Ureine                | 1.1 ± 0.02 | 3.8 ± 0.02 | 2.3 ± 0.02 | 3.5 ± 0.03 |
| Heart                 | 0.57 ± 0.01 | 0.15 ± 0.01 | 0.34 ± 0.01 | 0.1 ± 0.001 |
| Lung                  | 1.4 ± 0.02 | 1.54 ± 0.03 | 1.38 ± 0.02 | 0.21 ± 0.01 |
| Feces                 | 2.8 ± 0.01 | 2.3 ± 0.01 | 3.5 ± 0.01 | 3.33 ± 0.2 |
| Brain                 | 0.23 ± 0.02 | 0.07 ± 0.001 | 0.21 ± 0.01 | 0.09 ± 0.001 |

min: minute; H: healthy mice; T: solid tumor-bearing mice
pathway. $^{99m}$Tc-Lut, shows promise as a natural radiopharmaceutical tracer.

**Acknowledgments**

No acknowledgments were reported by the authors.

**Disclosure statement**

Authors claimed no conflict of interest.

**ORCID**

Hossam M. Hassan http://orcid.org/0000-0003-0174-4434
Abeer H. El maidomy http://orcid.org/0000-0002-4619-343X

**References**

Adams, M., Berset, C., Kessler, M., & Hamburger, M. (2009). Medicinal herbs for the treatment of rheumatic disorders—a survey of European herbal from the 16th and 17th century. *Journal of Ethnopharmacology*, 121(3), 343–359. https://doi.org/10.1016/j.jep.2008.11.010

Amin, A., El-Azony, K., & Ibrahim, I. (2009). Application of 99 Mo/99m Tc alumina generator in the labeling of metronidazole for diagnostic purposes. *Journal of Labelled Compounds and Radiopharmaceuticals: The Official Journal of the International Isotope Society*, 69(6), 1121–1124. https://doi.org/10.1016/j.jpharep.2017.05.010

Cai, Q., Rahn, R. O., & Zhang, R. (1997). Dietary flavonoids, quercetin, luteolin and genistein, reduce oxidative DNA damage and lipid peroxidation and quench free radicals. *Cancer Letters*, 119(1), 99–107. https://doi.org/10.1016/S0304-3835(97)00261-9

Chen, C.-Y., Peng, W.-H., Tsai, K.-D., & Hsu, S.-L. (2007). Luteolin suppresses inflammation-associated gene expression by blocking NF-kB and AP-1 activation pathway in mouse alveolar macrophages. *Life Sciences*, 81(23–24), 1602–1614. https://doi.org/10.1016/j.lfs.2007.09.028

Deng, C., Gao, C., Tian, X., Chao, B., Wang, F., Zhang, Y., Zou, J., & Liu, D. (2017). Pharmacokinetics, tissue distribution and excretion of luteolin and its major metabolites in rats: Metabolites predominate in blood, tissues and are mainly excreted via bile. *Journal of Functional Foods*, 35(1), 332–340. https://doi.org/10.1016/j.jff.2017.05.056

Elangovan, V., Sekar, N., & Govindasamy, S. (1994). Chemopreventive potential of dietary bioflavonoids against 20-methylcholanthrene-induced tumorigenesis. *Cancer Letters*, 87(1), 107–113. https://doi.org/10.1016/S0304-3835(94)00416-2

El maidomy, A. H., Mohammed, R., Hassan, M. H., Owis, I. A., Rateb, E. M., Khanfar, A. M., Krischke, M., Mueller, M. J., & Ramadan Abdelmohsen, U. (2019). Metabolomic Profiling and Cytotoxic Tetrahydrofurofuran Lignans Investigations from Premna odorata Blanco. *Metabolites*, 9(10), 223. https://doi.org/10.3390/metabo9100223

Essa, B., Sakr, T., Khedr, M. A., El-Essawy, F., & El-Mohdy, A. (2015). 99mTc-Amitrole as a novel selective imaging probe for solid tumor: In silico and preclinical pharmacological study. *European Journal of Pharmaceutical Sciences*, 76(1), 102–109. https://doi.org/10.1016/j.ejps.2015.05.002

Fitzpatrick, F., & Wynalda, M. (1981). Albumin-lipid interactions: Prostaglandin stability as a probe for characterizing binding sites on vertebrate albumins. *Biochemistry*, 20(3), 6129–6134. https://doi.org/10.1021/bi00524a033

Fons, F., Gargadennec, A., Gueffier, A., Roussel, J. L., & Andary, C. (1998). Effects of cinnamic acid on polyphenol production in Plantago lanceolata. *Phytochemistry*, 49(3), 697–702. https://doi.org/10.1016/S0031-9422(98)00210-6

Galvez, M. (2003). Cytotoxic effect of Plantago spp. on cancer cell lines. *Journal of Ethnopharmacology*, 88(2–3), 125–130. https://doi.org/10.1016/S0378-7417(03)00192-2

Ghosh, P., Sil, P., & Thakur, S. (1987). Spray reagent for the detection of coumarins and flavonoids on thin-layer plates. *Journal of Chromatography*. A, 403(4), 285–287. https://doi.org/10.1016/S0021-967X(00)96364-7

Ibrahim, I., El-Tawoosy, M., & Talaat, H. (2011). Labeling of tannic acid with technetium-99m for diagnosis of stomach ulcer. *ISRN Pharmaceutics*, 2011(5), 1–6. https://doi.org/10.5402/2011/578570

Kawashy, S., Gamal-el-din, E., Abdalla, M. F., & Saleh, N. A. M. (1994). Flavonoids of Plantago species in Egypt. *Biochemical Systematics and Ecology*, 22(7), 729–733. https://doi.org/10.1016/0305-1978(94)90058-2

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: An overview. *The Scientific World Journal*, 2013(2), 1–16. https://doi.org/10.1155/2013/162750

López-Lázaro, M. (2009). Distribution and biological activities of the flavonoid rutinol. <https://data_reviews_in_Medicinal_Chemistry>., 9(1), 31–59. https://doi.org/10.2174/13895570978001712

Makarova, M. (2011). [Bioavailability and metabolism of flavonoids].. *Voprosy Pitaniia*, 80(3), 4–12. https://europepmc.org/article/med/21842747

Manju, V., & Nalini, N. (2005). Chemopreventive potential of luteolin during colon carcinogenesis induced by 1,2-dimethylhydrazine. *The Italian Journal of Biochemistry*, 54(3–4), 268–275. https://www.europepmc.org/article/med/16688936

Manju, V., & Nalini, N. (2007). Protective role of luteolin in 1,2-dimethylhydrazine induced experimental colon carcinogenesis. *Cell Biochemistry and Function: Cellular Biochemistry and Its Modulation by Active Agents or Disease*, 25(2), 189–194. https://doi.org/10.1002/cbf.1305

Motaleb, M. A., El-Kolaly, M. T., Rashid, H. M., & El-Bary, A. A. (2011). Novel radiodinated sibutramine and fluoxetine as models for brain imaging. *Journal of Radioanalytical and Nuclear Chemistry*, 289(5), 915–921. https://doi.org/10.1007/s10967-011-1182-z

Oloumi, M. M., Vosough, D., Derakhshanfar, A., & Nematollahi, M. H. (2011). The healing potential of Plantago lanceolata ointment on collagenase-induced tendinitis in burros (Equus asinus). *Journal of Equine Veterinary Science*, 31(8), 470–474. https://doi.org/10.1016/j.jevs.2011.03.014

Özgen, U., Avşar, A., Terzi, Z., Kazaz, C., Asçi, A., Kaya, Y., & Seçen, H. (2011). Relationship between chemical structure and antioxidant activity of luteolin and its glycosides isolated from T. sipyleus subsp. sipyleus var. sipyleus. *Records of Natural Products*, 5(1), 12. https://core.ac.uk/download/pdf/25952993.pdf

Rashed, H., Marzouk, F., & Farag, H. (2016). 99mTc-zolmitriptan: Radiolabeling, molecular modeling, biodistribution and gamma scintigraphy as a hopeful radiopharmaceutical for...
lungs nuclear imaging. La Radiologia Medica, 121(7), 935–943. https://doi.org/10.1007/s11547-016-0677-7

Rennie, M. J. (1999). An introduction to the use of tracers in nutrition and metabolism. Proceedings of the Nutrition Society, 58(4), 935–944. https://doi.org/10.1077/S002966519900124X

Sarawek, S., Derendorf, H., & Butterweck, V. (2008). Pharmacokinetics of luteolin and metabolites in rats. Natural Product Communications, 3(1), 1934578X0800301218. https://doi.org/10.1177/1934578X0800301218

Walle, T., Otake, Y., Brubaker, J., Walle, U., & Halushka, P. (2001). Disposition and metabolism of the flavonoid chrysin in normal volunteers. British Journal of Clinical Pharmacology, 51(2), 143–146. https://doi.org/10.1111/j.1365-2125.2001.01317.x

Shipochliev, T., Dimitrov, A., & Aleksandrova, E. (1981). [Anti-inflammatory action of a group of plant extracts]. Veterinarno-meditsinski Nauki, 18(6), 87–94. https://europepmc.org/article/med/7199215

Singh, S. S. (2006). Preclinical pharmacokinetics: An approach towards safer and efficacious drugs. Current Drug Metabolism, 7(2), 165–182. https://doi.org/10.2174/1389200675541552

Souleles, C., & Laskaris, G. (1988). Flavonoids from Picnomon acarna. Planta Medica, 54(6), 47–48. https://doi.org/10.1055/s-2006-962332

Spies, H., & Pietenzsch, H.-J. (2007). Stannous chloride in the preparation of 99m Tc pharmaceuticals. Technetium-99m Pharmaceuticals, 5(7), 59–66. https://link.springer.com/chapter/10.1007/978-3-540-33990-8_3

Wawer, I., & Zielinska, A. (2001). 13C CP/MAS NMR studies of flavonoids. Magnetic Resonance in Chemistry, 39(7), 374–380. https://doi.org/10.1002/mrc.871

Ying, J., Li, X., Wang, J., & Yao, T. (2008). [Luteolin excretion after oral administration of Elsholtzia b tend extracts in rats]. Zhejiang Da Xue Xue Bao. Yi Xue Ban = Journal of Zhejiang University. Medical Sciences, 37(2), 139–145. https://europepmc.org/article/med/18422272