**Antiviral potential of green synthesized silver nanoparticles of** ***Lampranthus coccineus* and *Malephora lutea***

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**Abstract:** Viral and microbial infections constitute one of the most important life-threatening problems. The emergence of new viral and bacterial infectious diseases increases the demand for new therapeutic drugs. The aqueous and hexane extracts of *Lampranthus coccineus* and *Malephora lutea* F. Aizoaceaewere used for the synthesis of silver nanoparticles, and the early signs of SNPs synthesis were detected by a color change from yellow to dark brown color. The formation of SNPs was further confirmed using a transmission electron microscope (TEM), UV-Visible spectroscopy and Fourier transform infrared spectroscopy (FTIR). The TEM analysis of SNPs showed spherical nanoparticles with mean size ranges between 10.12 nm to 27.89 nm, and 8.91nm 14.48 nm for *Lampranthus coccineus* and *Malephora lutea* aqueous and hexane nano extracts respectively. The UV-Visible spectrophotometric analysis showed an absorption peak at λmax of 417 nm, which confirms the formation of SNPs. The antiviral activity of the synthesized nanoparticles was evaluated using MTT assay against HSV-1, HAV-10 virus and Coxsackie B4 virus. Metabolomics profiling was performed on the methanolic extract of *L. coccineus* and *M. lutea* and resulted in identifying 12 compounds, and then docking was done to further investigate the binding potential against different virus proteins on the molecular level.

**Keywords:** Silver nanoparticles, antiviral, metabolomics profiling*, Lampranthus coccineus*, *Malephora lutea*.

|  |  |
| --- | --- |
| **I** | **II**  |
| **III** | **IV** |

 **Figure S1 (I) Early sign for formation of SNPs in *Lampranthus coccineus* aqueous nano extract, (II) *Lampranthus coccineus* hexane nano extract, (III) *Malephora lutea* aqueous nano extract, (IV) *Malephora lutea* hexane nano extract observed as color change to yellowish brown after 24 hours incubation with 1 mM AgNO3 solution.**

**Table S1** Dereplication of the metabolomics of methanolic extract of *Lampranthus coccineus* and *Malephora lutea*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **M/Z** | **Retention time (min.)** | **M.wt.** | **Name** | **Molecular formula** | **References** |
| 613.234 | 1 | 612.226946 | Phoenicanthusine | C38H32N2O6 | (1) |
| 558.227 | 1.5 | 557.219805 | Uvarindole E | C36H31NO5 | (2) |
| 323.116 | 1.9 | 324.123503 | Cryptostyline I, (ξ)- 1,2,3,4-Tetradehydro | C19H18NO4 | (3, 4) |
| 353.0881 | 2 | 354.31100 | Chlorogenic acid | C16H18O9 | (5) |
| 303.090 | 2.5 | 304.09745 | 5, 6-Epoxy-7-megastigmene-3, 9-diol; (3,5,6E,7,9)-form, 9-ketone, 3-sulfate | C13H20O6S | (6) |
| 447.285 | 2.7 | 448.38000 | Luteoline-7-O- glucose | C21H20O11 | (4) |
| 312.124 | 2.8 | 311.116289 | Acronydine | C18H17NO4 | (3) |
| 311.168 | 4.7 | 312.175375 | 3, 7-Dimethyl-1-octanol; (R)-form, 4-methylbenzenesulfonyl | C17H28O3S | (7) |
| 294.182 | 4.7 | 295.18939 | Histamine; Nω-(2-Hydroxy-4-oxodecanoyl) | C15H25N3O3 | (3) |
| 326.187 | 4.8 | 327.194148 | Sophazrine | C19H25N3O2 | (8) |
| 339.199 | 5 | 340.20659 | 1-Dodecanol; 4-Methylbenzenesulfonyl | C19H32O3S | (9) |
| 295.227 | 5.7 | 296.234175 | Cinchonamine | C19H24N2O | (10) |

**Rt;** Retention time (min.), **M.wt.**; Molecular weight

**Table S2** The MNTC of *Lampranthus coccineus* and *Malephora lutea* extracts.

|  |  |
| --- | --- |
| **Name of the extract** | **MNTC (µg/ml)** |
| AgNO3 | 5.28 |
| *Lampranthus coccineus* aqueous extract | 781.2 |
| *Malephora lutea* aqueous extract | 390.6 |
| *Lampranthus coccineus* aqueous nano extract | 520.6/8.8 |
| *Malephora lutea* aqueous nano extract | 260.3/4.4 |
| *Lampranthus coccineus*hexane extract | 750 |
| *Malephora lutea*hexane extract | 750 |
| *Lampranthus coccineus*hexane nano extract | 46.87 |
| *Malephora lutea*hexane nano extract | 46.87 |

**MNTC:** Minimum nontoxic concentration



**Figure S2 (A) Control Vero cell, (B) MNTC of AgNO3 (5.28 µg/ml), (C) MNTC of *L. coccineus* aqueous extract (781.2 µg/ml), (D) MNTC of *M. lutea* aqueous extract (390.6 µg/ml), (E) MNTC of *L. coccineus* aqueous nano extract (520.6/8.8 µg/ml), (F) MNTC of *M. lutea* aqueous nano extract (260.3/4.4 µg/ml), (G) MNTC of *L. coccineus* hexane extract (750 µg/ml), (H) MNTC of *M.lutea* hexane extract (750 µg/ml), (I) MNTC of *L. coccineus* hexane nano extract (46.87 µg/ml), (J) MNTC of *M. lutea* hexane nano extract (46.87 µg/ml).**



**Figure S3 (k) Effect of AgNO3 against HSV-1 virus (5.28 µg/ml), (l) Effect of *Lampranthus coccineus* aqueous nano extract against HSV-1 virus (520.6 µg/ml), (m) Effect of *Malephora lutea* hexane extract on COXB4 virus (46.44 µg/ml), (n) Effect of *Malephora lutea* hexane nano extract against COXB4 virus (29.04 µg/ml).**

**Table S3** Cytotoxic effect of *Lampranthus coccineus* and *Malephora lutea* extracts on HAV-10.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero Cells** |  | 0.23 | 0.241 | 0.227 | 0.232667 | 100 | 0 | ----------- | ----------- | ------------ |
| **HAV-10** |  | 0.094 | 0.106 | 0.099 | 0.099667 | 42.83661 | 57.16339 | 100 | 0 | ------------ |
| **AgNO3** | 5.28 | 0.123 | 0.136 | 0.152 | 0.137 | 58.88244 | 41.11756 | 71.92989 | 28.070111 | ------------ |
| ***Lampranthus coccineus* aqueous extract** | 781.2 | 0.089 | 0.097 | 0.096 | 0.094 | 40.40109 | 59.59891 | 104.2606 | 0 | ----------- |
| ***Malephora lutea* aqueous extract** | 390.6 | 0.105 | 0.102 | 0.098 | 0.101667 | 43.69621 | 56.30379 | 98.49624 | 1.50376 | ----------- |
| ***Lampranthus coccineus* nano aqueous extract** | 520.6/8.8 | 0.099 | 0.105 | 0.087 | 0.097 | 41.69048 | 58.30952 | 102.005 | 0 | ----------- |
| ***Malephora lutea* nano aqueous extract** | 260.3/4.4 | 0.1 | 0.103 | 0.104 | 0.102333 | 43.98275 | 56.01725 | 97.99498 | 2.0050158 | ----------- |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero cells** |  | 0.224 | 0.219 | 0.226 | 0.223 | 100 | 0 | ----------- | ----------- | ---------- |
| **HAV-10** |  | 0.101 | 0.097 | 0.099 | 0.099 | 44.39462 | 55.60538 | 100 | 0 | ---------- |
| ***Lampranthus coccineus* hexane extract** | 1500 | 0.182 | 0.19 | 0.179 | 0.183667 | 82.36173 | 17.63827 | 31.72043 | 68.279569 | ---------- |
| 750 | 0.099 | 0.101 | 0.095 | 0.098333 | 44.09567 | 55.90433 | 100.5376 | 0 |
| ***Malephora lutea* hexane extract** | 1500 | 0.159 | 0.162 | 0.171 | 0.164 | 73.5426 | 26.4574 | 47.58065 | 52.419353 | ---------- |
| 750 | 0.099 | 0.1 | 0.097 | 0.098667 | 44.24514 | 55.75486 | 100.2688 | 0 |
| ***Lampranthus coccineus* hexane nano extract** | 46.87 | 0.22 | 0.218 | 0.223 | 0.220333 | 98.80419 | 1.195815 | 2.150538 | 97.849462 | 11.71 |
| 23.43 | 0.206 | 0.197 | 0.201 | 0.201333 | 90.28401 | 9.715994 | 17.47312 | 82.526881 |
| 11.71 | 0.184 | 0.175 | 0.168 | 0.175667 | 78.77429 | 21.22571 | 38.17204 | 61.827956 |
| 5.85 | 0.169 | 0.11 | 0.105 | 0.128 | 57.3991 | 42.6009 | 76.6129 | 23.387095 |
| ***Malephora lutea* hexane nano extract** | 46.87 | 0.2 | 0.193 | 0.204 | 0.199 | 89.23767 | 10.76233 | 19.35484 | 80.645160 | 31.38 |
| 23.43 | 0.162 | 0.132 | 0.15 | 0.148 | 66.36771 | 33.63229 | 60.48387 | 39.516127 |
| 11.71 | 0.103 | 0.101 | 0.099 | 0.101 | 45.29148 | 54.70852 | 98.3871 | 1.6129011 |
| 5.85 | 0.098 | 0.096 | 0.094 | 0.096 | 43.04933 | 56.95067 | 102.4194 | 0 |

O.D.: Optical density

**Table S4** Cytotoxic effect of *Lampranthus coccineus* and *Malephora lutea* extracts on HSV-1 virus.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero cells** | --------- | 0.23 | 0.241 | 0.227 | 0.232667 | 100 | 0 | --------- | --------- | --------- |
| **HSV-1** | --------- | 0.123 | 0.124 | 0.122 | 0.123 | 52.86525 | 47.13475 | 100 | 0 | --------- |
| **AgNO3** | 5.28 | 0.186 | 0.187 | 0.172 | 0.181667 | 78.08012 | 21.91988 | 46.50472 | 53.495281 | 5.28 |
| 2.64 | 0.142 | 0.131 | 0.13 | 0.134333 | 57.73631 | 42.26369 | 89.66568 | 10.334322 |
| 1.32 | 0.123 | 0.117 | 0.125 | 0.121667 | 52.29219 | 47.70781 | 101.2158 | 0 |
| ***Lampranthus coccineus* aqueous extract**  | 781.2 | 0.152 | 0.146 | 0.137 | 0.145 | 62.32083 | 37.67917 | 79.93926 | 20.060735 | --------- |
| ***Malephora lutea* aqueous extract** | 390.6 | 0.163 | 0.156 | 0.171 | 0.163333 | 70.20047 | 29.79953 | 63.22199 | 36.778008 | --------- |
| 195.3 | 0.132 | 0.144 | 0.139 | 0.138333 | 59.4555 | 40.5445 | 86.01827 | 13.981727 |
| ***Lampranthus coccineus* aqueous nano extract** | 520.6/8.8 | 0.177 | 0.183 | 0.174 | 0.178 | 76.50419 | 23.49581 | 49.84817 | 50.151827 | 520.6 |
| 260.3/4.4 | 0.136 | 0.134 | 0.125 | 0.131667 | 56.59018 | 43.40982 | 92.09728 | 7.9027189 |
| ***Malephora lutea* aqueous nano extract** | 260.3/4.4 | 0.142 | 0.123 | 0.138 | 0.134333 | 57.73631 | 42.26369 | 89.66568 | 10.334322 | --------- |

O.D.: Optical density

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero cells** | --------- | 0.224 | 0.219 | 0.226 | 0.223 | 100 | 0 | --------- | --------- | --------- |
| **HSVI** |  | 0.113 | 0.108 | 0.119 | 0.113333 | 50.82212 | 49.17788 | 100 | 0 | --------- |
| ***Lampranthus coccineus* hexane extract** | 1500 | 0.116 | 0.096 | 0.118 | 0.11 | 49.32735 | 50.67265 | 103.0395 | 0 | --------- |
| 750 | 0.116 | 0.116 | 0.108 | 0.113333 | 50.82212 | 49.17788 | 100 | 0 |
| ***Malephora lutea* hexane extract** | 1500 | 0.126 | 0.12 | 0.106 | 0.117333 | 52.61584 | 47.38416 | 96.35258 | 3.647421 |  |
| 750 | 0.113 | 0.115 | 0.113 | 0.113667 | 50.9716 | 49.0284 | 99.69604 | 0.303956 |
| ***Lampranthus coccineus* hexane nano extract** | 46.87 | 0.2 | 0.216 | 0.218 | 0.211333 | 94.76831 | 5.231689 | 10.6383 | 89.361702 | 36.36 |
| 23.43 | 0.142 | 0.168 | 0.155 | 0.155 | 69.50673 | 30.49327 | 62.00608 | 37.993924 |
| 11.71 | 0.106 | 0.096 | 0.108 | 0.103333 | 46.33782 | 53.66218 | 109.1185 | 0 |
| 5.85 | 0.115 | 0.108 | 0.116 | 0.113 | 50.67265 | 49.32735 | 100.3039 | 0 |
| ***Malephora lutea* hexane nano extract** | 46.87 | 0.114 | 0.106 | 0.112 | 0.110667 | 49.62631 | 50.37369 | 102.4316 | 0 | --------- |
| 23.43 | 0.116 | 0.118 | 0.109 | 0.114333 | 51.27055 | 48.72945 | 99.08814 | 0.91185 |

O.D.: Optical density

**Table S5** Cytotoxic effect of *Lampranthus coccineus* and *Malephora lutea* extracts on CoxB4 virus.

O.D.: Optical density

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero cells** | -------- | 0.23 | 0.241 | 0.227 | 0.232667 | 100 | 0 | -------- | -------- | -------- |
| **CoxB4** | -------- | 0.113 | 0.108 | 0.102 | 0.107667 | 46.27501 | 53.72499 | 100 | 0 | -------- |
| **AgNO3** | 5.28 | 0.13 | 0.12 | 0.124 | 0.124667 | 53.58159 | 46.41841 | 86.39215 | 13.607851 | -------- |
| ***Lampranthus coccineus* aqueous extract** | 781.2 | 0.113 | 0.114 | 0.109 | 0.112 | 48.13747 | 51.86253 | 96.52453 | 3.4754705 | -------- |
| ***Malephora lutea* aqueous extract** | 390.6 | 0.103 | 0.097 | 0.096 | 0.098667 | 42.40682 | 57.59318 | 107.1902 | 0 | -------- |
| ***Lampranthus coccineus* aqueous nano extract** | 520.6/8.8 | 0.123 | 0.118 | 0.12 | 0.120333 | 51.71912 | 48.28088 | 89.85849 | 10.14151 | -------- |
| ***Malephora lutea* aqueous nano extract** | 260.3/4.4 | 0.12 | 0.125 | 0.11 | 0.118333 | 50.85953 | 49.14047 | 91.45834 | 8.5416611 | -------- |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Dilution****µg/ml** | **O.D** | **Mean O.D** | **Viability** | **Toxicity** | **Viral activity %** | **Antiviral effect %** | **IC50****µg/ml** |
| **Control vero cells** | -------- | 0.224 | 0.219 | 0.226 | 0.223 | 100 | 0 | -------- | -------- | -------- |
| **CoxB4** | -------- | 0.12 | 0.103 | 0.108 | 0.110333 | 49.47683 | 50.52317 | 100 | 0 |  |
| ***Lampranthus coccineus* hexane extract** | 1500 | 0.142 | 0.168 | 0.152 | 0.154 | 69.0583 | 30.9417 | 61.2426 | 38.757397 | -------- |
| 750 | 0.11 | 0.112 | 0.109 | 0.110333 | 49.47683 | 50.52317 | 100 | 0 |
| ***Malephora lutea* hexane extract** | 1500 | 0.158 | 0.166 | 0.179 | 0.167667 | 75.18685 | 24.81315 | 49.11242 | 50.887575 | 46.44 |
| 750 | 0.109 | 0.114 | 0.113 | 0.112 | 50.22422 | 49.77578 | 98.52071 | 1.4792920 |
| ***Lampranthus coccineus* hexane nano extract** | 46.87 | 0.218 | 0.211 | 0.209 | 0.212667 | 95.36622 | 4.633782 | 9.171597 | 90.828402 | 12.74 |
| 23.43 | 0.201 | 0.216 | 0.207 | 0.208 | 93.27354 | 6.726457 | 13.31361 | 86.686390 |
| 11.71 | 0.164 | 0.179 | 0.18 | 0.174333 | 78.17638 | 21.82362 | 43.19527 | 56.804734 |
| 5.85 | 0.125 | 0.136 | 0.127 | 0.129333 | 57.99701 | 42.00299 | 83.13609 | 16.863907 |
| ***Malephora lutea* hexane nano extract** | 46.87 | 0.206 | 0.213 | 0.209 | 0.209333 | 93.87145 | 6.12855 | 12.13018 | 87.869822 | 29.04 |
| 23.43 | 0.153 | 0.148 | 0.163 | 0.154667 | 69.35725 | 30.64275 | 60.65089 | 39.349113 |
| 11.71 | 0.13 | 0.121 | 0.12 | 0.123667 | 55.4559 | 44.5441 | 88.16568 | 11.834321 |
| 5.85 | 0.105 | 0.113 | 0.11 | 0.109333 | 49.0284 | 50.9716 | 100.8876 | 0 |

O.D.: Optical density

**Table S6** The scores of re-docking the co-crystallized ligands and the top-scoring compounds of the *Lampranthus coccineus* and *Malephora lutea* methanolic extract in the active sites of thymidine kinase of herpes simplex virus type I (PDB ID: 1KI2), 3c proteinase of hepatitis A virus (PDB ID: 1QA7) and 3c protease of coxsackievirus B3 (PDB ID: 2ZU3).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Ligand** | **1KI2** | **1QA7** | **2ZU3** |
| Cocrystallized | Ganciclovir | -5.85 |  |  |
|  | N-(iodoacetyl)-L-valyl-L-phenylalaninamide |  | -7.13 |  |
|  | N-[(benzyloxy)carbonyl]-3-[(2,2-dimethylpropanoyl)amino]-L-alanyl-N-[(1R)-4-oxo-1-{[(3S)-2-oxopyrrolidin-3-yl]methyl}pentyl]-L-leucinamide |  |  | -7.18 |
| Compounds from *Lampranthus coccineus* and *Malephora lutea* methanolic extract | 3,7-Dimethyl-1-octanol; (R)-form, 4-Methylbenzenesulfonyl | -9.29 | -7.19 | -6.4 |
| 1-Dodecanol; 4-Methylbenzenesulfonyl | -9.16 | -6.58 | -6.04 |
| Chlorogenic acid | -7.92 | -8.32 | -6.37 |
| Luteoline-7-glucose | -6.66 | -8.13 | -6.74 |
| Sophazrine | -6.92 | -6.02 | -7.26 |
| Cryptostyline I, 1,2,3,4-Tetradehydro | -8.49 | -7.11 | -6.22 |
| Histamine; Nω-(2-Hydroxy-4-oxodecanoyl) | -8.41 | -6.27 | -5.6 |
| 5,6-Epoxy-7-megastigmene-3,9-diol; (3,5,6,7E,9)-form, 9-Ketone, 3-sulfate | -8.34 | -7.57 | -5.47 |
| Cinchonamine | -7.3 | -6.42 | -6.51 |
| Acronydine | -7.25 | -7.02 | -6.43 |

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