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NOVEL SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) FORMULATIONS TO IMPROVE BIOACTIVITIES OF ORGANIC SOLVENTS CRUDE EXTRACTS OF *Pandanus tectorius*

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Pandanus tectorius is a coastal plant that belongs to Pandanaceae family and grows in semi-natural vegetation throughout the tropical and subtropical regions. The fruits and leaves extracts of *P. tectorius* have many bioactivities. However, the extracts and bioactive compounds have semi-polar properties and limited solubility. The effect of bioactivities probably is not optimum, and bioavailability might be affected in oral administration. Hence, modification was needed to increase the solubility and bioactivities of the extracts. Self-nanoemulsifying drug delivery system (SNEDDS) might be the best carrier to improve solubility and bioactivities. PT-SNEDDSs (*P. tectorius*-SNEDDS) were formulated and optimized through solubility test, optimization of surfactant and co-surfactant, and construction of ternary phase diagram. The characterizations were carried out by robustness to dilution, self-emulsification time, thermodynamic stability, optical clarity, FTIR analysis, particle size, and zeta potential. The antioxidant, antiatherosclerosis, and cytotoxicity were also determined. The results showed that the PT extracts were successfully formulated into novel SNEDDS formulations including PTFM-SNEDDS (16% caprylic triglyceride, 50% kolliphor RH-40, and 34% propylene glycol), PTLM-SNEDDS (18% caprylic triglyceride, 49% kolliphor RH-40, and 33% propylene glycol),

PTLEA-SNEDDS (35% mixture of oleic acid and triglycerides (1:2), 49% tween 80, and 33% PEG400), and PTLH-SNEDDS (25% mixture of oleic acid and triglycerides (1:2), 50% tween 80, and 25% PEG400). The PT-SNEDDSs had grade A formulations, nanometric size <100 nm, and PDI value <0.7 indicating uniform globule size distribution. The SNEDDS could significantly improve (p<0.05) antioxidant and anti-atherosclerosis activity of the extracts. The antioxidant activity of PTFM-SNEDDS, PTLM-SNEDDS, and PTLH-SNEDDS were two times higher and PTLEA-SNEDDS was six times higher compared to extracts. Besides that, PT-SNEDDSs inhibited HMGCR enzyme activity as great as Simvastatin and Atorvastatin drugs at the same concentration. The PTLM-SNEDDS, PTLEA-SNEDDS, and PTLH-SNEDDS had cytotoxicity properties against HepG2 cells, while the PTFM-SNEDDS was not cytotoxic. This indicated that PTFM-SNEDDS was safe to be used as a drug to prevent hypercholesterolemia and atherosclerosis. These findings proved that Self-nanoemulsifying Drug Delivery System (SNEDDS) can be used as a carrier for novel PT-SNEDDS and improve the solubility and bioactivities of *P. tectorius* extracts.

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FORMULASI NOVEL SISTEM PENYAMPAIAN UBAT NANO EMULSI UNTUK MENINGKATKAN BIOAKTIVITI DARI EKSTRAK KASAR PELARUT ORGANIK *Pandanus tectorius*

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Pandanus tectorius ialah tumbuhan pantai yang tergolong dalam keluarga Pandanaceae dan tumbuh dalam tumbuh-tumbuhan separa semulajadi di seluruh Kawasan tropika dan subtropika. Ekstrak buah dan daun *P. tectorius* mempunyai banyak bioaktiviti. Tetapi, ekstrak tumbuhan dan sebatian menunjukkan sifat semi-polar dan keterlarutan terhad. Bioaktiviti ekstrak mungkin tidak memberikan kesan maksimum dan bioketersediaan mungkin terhad untuk pemberian oral. Oleh itu, pengubahsuaian ekstrak diperlukan untuk meningkatkan keterlarutan dan bioaktiviti. Sistem Penyampaian Ubat Pengemulsi Nano (SNEDDS) mungkin formulasi terbaik untuk meningkatkan keterlarutan dan bioaktiviti. PT-SNEDDSs (*P. tectorius*- Sistem Penyampaian Ubat Pengemulsi Nano) diformulasi dan dioptimumkan melalui uji keterlarutan, optimasi surfaktan dan ko-surfaktan, dan rajah fasa ternari. Kemudian, mereka dicirikan untuk mengetahui keteguhannya kepada pencairan, masa pengemulsi diri, kestabilan termodinamik, kejelasan optik, analisis FTIR, saiz zarah, dan potensi zeta. Aktiviti antioksidan, anti-aterosklerosis, dan analisis sitotoksik juga ditentukan. Keputusan menunjukkan bahawa ekstrak *P. tectorius* berjaya diformulasi menjadi formulasi novel SNEDDS termasuk PTFM-SNEDDS (16% trigliserida kaprilik, 50% kolliphor RH-40, dan 34% propilena glikol), PTLM-SNEDDS (18% trigliserida

kaprilik, 49% kolliphor RH-40, dan 33% propilena glikol), PTLEA-SNEDDS (35% campuran asid oleik dan trigliserida kaprilik (1:2), 49% tween 80, and 33% PEG400), dan PTLH-SNEDDS (25% campuran asid oleik dan trigliserida kaprilik (1:2), 50% tween 80, dan 25% PEG400). PT-SNEDDS mempunyai rumusan gred A, saiz nanometrik <100 nm, dan nilai index polidispersi <0.7 menunjukkan taburan saiz globul seragam. SNEDDS boleh meningkatkan aktiviti antioksidan dan anti-aterosklerosis ekstrak *P. tectorius* dengan ketara (p<0.05). Aktiviti antioksidan PTFM-SNEDDS, PTLEA-SNEDDS, dan PTLH-SNEDDS telah meningkat dua kali dan PTLEA-SNEDDS meningkat enam kali daripada ekstrak. Selain itu, PT-SNEDDS menghalangi aktiviti enzim HMGCR sehebat ubat Simvastatin dan Atorvastatin pada kepekatan yang sama, PTLM-SNEDDS, PTLEA-SNEDDS, dan PTLH-SNEDDS mempunyai sifat sitotoksik terhadap sel HepG2, manakala PTFM-SNEDDS bukan sitotoksik. Ini menunjukkan bahawa PTFM-SNEDDS aman digunakan sebagai ubat untuk penyakit seperti mencegah hiperkolesterolemia dan aterosklerosis. Penemuan ini membuktikan bahawa Sistem Penyampaian Ubat Pengemulsi Nano (SNEDDS) boleh digunakan sebagai pembawa untuk novel PT-SNEDDS dan meningkatkan keterlarutan dan bioaktiviti ekstrak *P. tectorius.*