Therapeutic potential of rosmarinic acid against myocardial infarction comorbid depression in rats

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By

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Chapter 5: Summary, conclusions and scope for further work

5.1 Summary and conclusions

Overall, our main finding revealed that MS and CUS independently may lead to cardiac abnormalities. These stressors also have the good validities (face, construct, and predictive validity) to become a significant model for induction of depression as well as cardiac anomalies. So, we have used to find out the therapeutic effect of rosmarinic acid as an antidepressant as well as cardioprotective drug. Similarly, instead of conventional drugs several researchers are focusing on herbal medicines. Because, the conventional medicines for depression are limited with dangerous life-threatening adverse effects. As we discussed in each chapter that rosmarinic acid produce therapeutic effects *via* improving immobility period, anhedonia symptoms, corticosterone, MMP-2, TNF-α, IL-6, AST, ALT, lipid peroxidation, and alleviating SOD, catalase activity, GSH level, BDNF, 5-HT, ECG parameters (QRS complex and T wave), cardiac biomarkers (CKMB, LDH, cTn-I), pro-inflammatory cytokines (IL-6 and TNF-α), and anti-inflammatory cytokine (IL-10) level. In result section, all findings stated that rosmarinic acid has therapeutic property against myocardial infarction comorbid depression.

The main outcome of the current research is that rosmarinic acid dose-dependently enhanced cardioprotective activity against stress models in rats. In addition, rosmarinic acid exhibited antidepressant activity, anti-oxidant activity, BDNF modulatory, anti-inflammatory, and antiplatelet aggregatory activity. In our study we also performed HPLC (corticosterone level in blood plasma), RT-PCR (IL-10), and in-silico study (Network pharmacology and docking), docking (MMP2, TrkB for BDNF, STAT3 for IL10, TXA2 for thrombin, and P2Y12 for ADP) to validate all findings. Using these in-silico studies we found various inflammatory pathways including TNF signalling

and NF-kB signalling are involved in myocardial infarction comorbid depression. Whereas, docking finding stated the good binding energy of rosmarinic acid with abovementioned receptors than reference drugs.

Major findings of the present research work are as follows:

- Rosmarinic acid at dose of 25 and 50 mg/kg was found efficacious against myocardial infarction comorbid depression through alleviation of inflammation and oxidative stress.
- Rosmarinic acid can be used as cardioprotective agent in depression induced cardiac abnormalities.
- Maternal separation itself cause ST elevation.
- MS received CUS exposure may further increase the severity of cardiac disease.

Rosmarinic acid treatments significantly reversed the cardiac dysfunction parameters induced by MS and CUS exposure in Wistar rats.

5.2 Scope for further work

The combination dual stress models for developing cardiac disease followed by depressive-like behavior in rats may become a major model for developing antidepressant and cardioprotective drugs in this comorbidity. Rosmarinic acid was based on the potential of antioxidative, anti-inflammatory, and BDNF modulatory properties. The present study revealed the cardioprotective effect of rosmarinic acid against stressors may be a major therapeutic approach in upcoming researches. In the future, evaluation of rosmarinic acid in patient with cardiac disease comorbid depression is warranted to translate the results into clinical settings. Since, heart attack is the greatest contributor to deaths due to chronic stress, the good efficacy of

rosmarinic acid in stressor models of rats are further warranted. In vitro studies that evaluate the expression of BDNF, inflammation, monoamines *via* western blot and pharmacologic inhibition studies which may evaluate the inhibitory activity of RA on multiple targets are further warranted. However, for more validation to our studies, works on antibody levels are warranted.