Basic Medical Research

Effects of methotrexate, *Moringa oleifera*, and *Andrographis paniculata* extracts on the myocardial and aortic tissue of streptozotocin-nicotinamide-induced hyperglycemic rats

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ABSTRACT

BACKGROUND Methotrexate (MTX) could lower glucose levels in type 1 diabetes mellitus, while *Moringa oleifera* and *Andrographis paniculata* supplementations have similar effects on hyperglycemia. This study aimed to analyze the effects of MTX, *M. oleifera*, and *A. paniculata* leaf extracts on the myocardial interleukin (IL)-6 and the histopathology of the left ventricle and aorta.

METHODS 49 rats were divided equally into 7 groups: negative control and diabetic induced by streptozotocin-nicotinamide (STZ-NA) injection consisting of positive control (STZ-NA only), *M. oleifera* (500 mg/kgBW/day), *A. paniculata* (500 mg/kgBW/day), MTX (7 mg/kgBW/week), MTX (7 mg/kgBW/week)+*M. oleifera* (500 mg/kgBW/day), and MTX (7 mg/kgBW/week)+*A. paniculata* (500 mg/kgBW/day). We analyzed oral MTX, *M. oleifera*, and *A. paniculata* leaf extracts' effects on random blood glucose, myocardial IL-6, and cardiac histopathology of STZ-NA-induced hyperglycemic male rats. Data were analyzed using Wilcoxon and Kruskal–Wallis tests.

RESULTS Myocardial IL-6 in the *M. oleifera* group was significantly lower compared to the positive control group ($p = 0.041$). Compared to the positive control group, the myocardial necrosis and aortic intima–media thickness in the MTX+*A. paniculata* group were significantly reduced ($p = 0.005$ and 0.001, respectively).

CONCLUSIONS MTX, *M. oleifera*, and *A. paniculata* showed antihyperglycemic effect, both individually and in combination. A. *paniculata* leaf extract had a significant cardioprotective effect in STZ-NA-induced hyperglycemia.

KEYWORDS *Andrographis paniculata*, cardiovascular disease, diabetes, methotrexate, *Moringa oleifera*

Diabetic cardiomyopathy (DCM) affects approximately 26 million people worldwide, and its prevalence is constantly increasing.[1–3] The prevalence of heart failure among patients with diabetes mellitus (DM) ranges from 9% to 22%, which is 4 times higher than that among the general population, with a higher incidence in patients with DM aged ≥60 years.[2] Hyperglycemia in patients with DM increases oxidative stress within the vascular system and myocardium, followed by the formation of advanced glycation end products, which is cross-link collagen molecules, increasing fibrosis and myocardial stiffness and impairing cardiac relaxation.[2,4] Quercetin and rutin, bioflavonoid substances found in *Moringa oleifera*, and andrographolide in *Andrographis paniculata* possess cardioprotective effects.[4,5]

Methotrexate (MTX) can reduce myocardial necrosis;[6] however, a more detailed investigation should be done because it also induces myocardial necrosis[4] and lower blood glucose in patients with type 1 DM (T1DM).[7,8] Furthermore, *M. oleifera* and *A. paniculata* leaf extracts significantly lower the blood glucose level in animal models induced with streptozotocin-nicotinamide (STZ-NA).[9,10] The kaempferol in *M. oleifera* extract possesses a hypoglycemic effect by increasing skeletal muscle glucose uptake through phosphoinositide 3-kinase (PI3K) and protein kinase C (PKC) pathways,[11] whereas phytochemicals in the *A. paniculata* leaf extracts have andrographolide that increases glucose transporter type 4 (GLUT4) expression and andrographolide lipoic acid that increases insulin secretion.[10,12] Various studies have reported the cardioprotective effect of *M. oleifera* and *A. paniculata* separately.[5,13] However, their effect in the same study and when combined with MTX as a therapy has yet to be reported. Therefore, this study aimed to analyze the effects of MTX, *M. oleifera*, and *A. paniculata* leaf extracts on myocardial interleukin (IL)-6 levels and the histopathology of the left ventricle (LV) and aorta in DM-induced male rats to determine any potential cardioprotective and antihyperglycemic effects to reduce the risk of DCM.

METHODS

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Airlangga (No. 1/EC/KEPK/FKUA/2022). The sample size was determined using Mead's resource equation.[14] Experimental animal care, intervention, random data collection of body weight and blood sugar levels, and sacrifice were conducted at the Pharmacology Laboratory of the Faculty of Medicine, Universitas Airlangga.

Experimental

Forty-nine male rats *(Rattus norvegicus)*, aged 2–3 months, and weighing 150–250 g, were acclimatized before experimentation and given *ad libitum* standard rodent food (Pokphand CP 593, Charoen Pokphand Indonesia, Indonesia) and drinking water. DM was induced by an intraperitoneal injection of 50 mg/kg STZ (Sigma-Aldrich, Japan), preceded by an intraperitoneal injection of 110 mg/kg NA.[15]

The rats were divided equally into seven groups: negative control and diabetic induced by STZ-NA injection consisting of positive control (STZ-NA only), *M. oleifera*, *A. paniculata*, MTX, MTX+*M. oleifera*, and MTX+*A. paniculata*. MTX (Rheu-Trex, Kalbe Farma, Indonesia) was administered orally once a week at a dose of 7 mg/kg, whereas M. *oleifera* extract (Sido Muncul, batch number EH00012, Indonesia) and *A. paniculata* extracts (Jamu Iboe, batch number SB1081A, Indonesia) were administered orally daily at a dose of 500 mg/kg for 28 days.[16,17] One animal died in each *A. paniculata*, MTX+*M. oleifera*, and MTX+*A. paniculata* groups.

During the treatment period, the rats' body weights were measured 12 times (thrice weekly for 4 weeks) using a triple beam scale (Ohaus Corporation, USA). To measure random blood glucose (RBG), the blood samples were collected through the excision of the blood vessels in the tail. RBG levels were measured 6 times (once before STZ-NA injection, once after STZ-NA injection, and the remaining once weekly during the treatment period) using Model ET-301 glucometer (Guangzhou Easy Touch Technology Co., Ltd, China).

Tissue extraction and IL-6 measurement

After 28 days of treatment, the rats were sacrificed on Day 29 using an overdose of ether.[18] Then, the heart and aorta attached were extracted. The heart was cut into two pieces at the anterior interventricular sulcus. The right ventricle was processed to measure the IL-6 level using the enzyme-linked immunosorbent assay (ELISA) technique.[19] Right ventricular tissue was sliced into pieces and submerged in a collagenase type IV and DNase solution (Bioenzy, Cat. No. BZ-08185310-EB, Indonesia) to degrade it into component cells. After centrifugation, the cells were resuspended in a growth medium, and the supernatant was discarded. The red blood cells were lysed by dissolving the resulting cell pellets in a solution. A complete culture medium was then applied to the cell pellets after centrifugation, and the supernatant was removed. ELISA was used to detect IL-6 levels, in which samples and standards were added to ELISA plates and incubated. Subsequently, the plate was cleaned, and a color development solution was added, followed by additional incubation. This process was terminated by adding a stop solution. The samples were then scanned using an ELISA reader at a wavelength of 450

nm to determine IL-6 levels. Myocardial IL-6 level was measured using a rat IL-6 measurement kit (Bioenzy, Cat. No BZ-08185310-EB).

Myocardial necrotic score and aortic intima–media thickness (IMT)

The remaining heart tissue was used for necrotic score measurements at the LV and aortic IMT measurements. The heart was immersed in a fixative solution of 10% formalin buffer prior to the histological process. Paraffin blocks of the LV and aorta were then sliced at 5 µm thickness and stained using hematoxylin and eosin for the myocardium of the LV and Mallory-Azan for the aorta. All histological analyses were performed from 10 visual fields at 200× magnification using a light microscope (Olympus CX23 light microscope, Olympus Company, Japan). Images of the myocardium of the LV and aortic walls were processed using CellSense software (Olympus cellSens Software [RRID: SCR_014551], Olympus Company). Rocha necrosis score was used to calculate myocardial necrosis as follows: 0 = no damage, 1 = early necrotic changes and scattered neutrophilic infiltrate, 2 = one clear area of necrosis, 3 = two or more separate areas of necrosis but <50% of the ventricular wall, and 4 = extensive area of necrosis of >50% of the myocardial thickness.[20]

The myocardial necrotic score was analyzed by two observers blinded to the animal grouping and sample number. The mean necrotic score was used for statistical analysis. The necrotic score was analyzed as previously described.[20] IMT analysis was performed at 200× magnification in 10 visual fields, and three random measurements of the aortic wall thickness (the distance between the endothelial cell layer and the transitional zone of the medial-adventitial layer) were taken.[21] Further attributes have been previously described.[22–24]

Statistical analysis

All data were analyzed using SPSS software version 17 for Windows (SPSS Inc., USA).[25] Data were tested for normality using Shapiro–Wilk and for homogeneity using Levene test. The body weight, RBG level, myocardial IL-6 level, Rocha necrosis score, and aortic IMT were compared among the seven groups. Statistical significance was set at $p<0.05$. The post-hoc Kruskal–Wallis test was performed using the Mann–Whitney *U* test.

RESULTS

Body weight in the negative control group was significantly increased but decreased in the positive control group (Figure 1a). All rats induced with STZ-NA had high RBG (Figure 1b).

Figure 2 shows the myocardial tissue IL-6 levels and histopathological image of the myocardium. Myocardial IL-6 levels in the negative control group were significantly lower than those in all the hyperglycemic groups ($p<0.001$). The post-hoc test (not shown) showed significant differences among the groups ($p = 0.041$). The Rocha necrosis score was significantly higher in the MTX+*M. oleifera* group ($p = 0.002$) (Figure 2a). The score was significantly lower in the MTX+*A. paniculata* group than in the positive control group ($p = 0.005$, not shown). Myocardial necrosis in each experimental group is shown in Figure 2.

In the negative control group, no necrotic centers, inflammatory cell infiltration, and/or interstitial edema

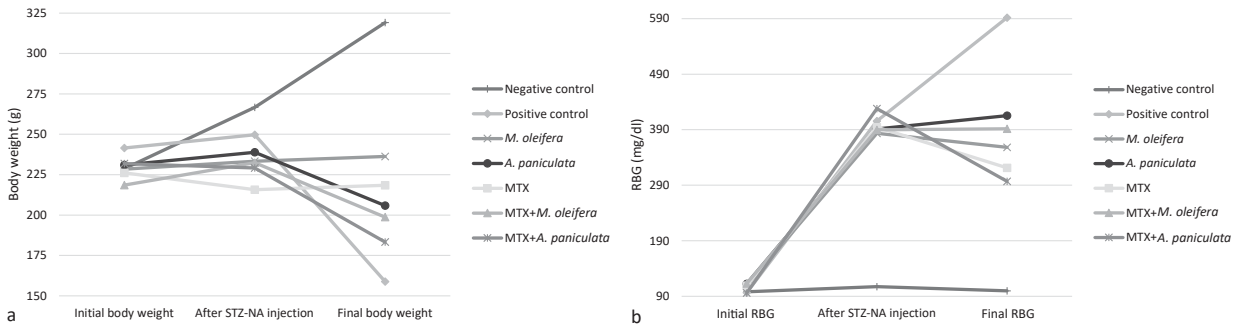

Figure 1. Body weight and RBG of the experimental rats. Body weight changes (a) and RBG levels (b) in hyperglycemic rats following *M. oleifera* treatment. Diabetic groups were induced by STZ-NA injection. MTX=methotrexate; RBG=random blood glucose; STZ-NA=streptozotocin-nicotinamide

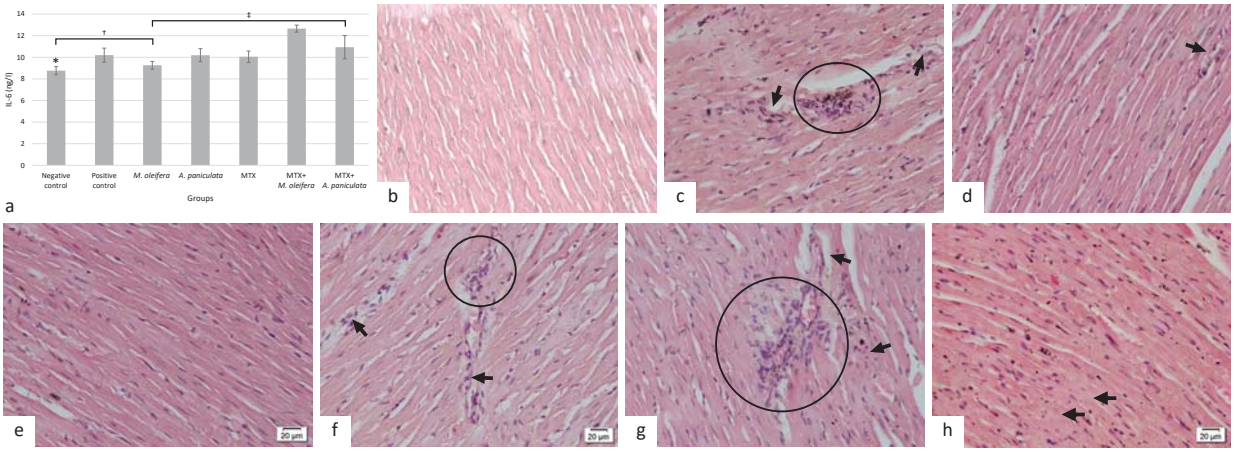

Figure 2. Histopathology of LV myocardium in all groups. (a) Myocardial IL-6 concentration in all experimental groups (mean [SD]); (b) negative control group myocardial tissue showing a normal appearance with regular fibers, without any apparent necrosis or inflammatory cell infiltration; (c) positive control group showing necrotic centers with inflammatory cell infiltration (in circle) and interstitial edema (arrows); (d) *M. oleifera* group showing mild interstitial edema and inflammatory cell infiltrations (arrow); (e) *A. paniculata* group showing near-normal appearance, with mild edema without inflammatory cell infiltration or necrotic centers; (f) MTX group showing necrotic centers (arrows) described as cardiomyocyte cytoplasmic disintegration and inflammatory cell infiltration, with interstitial edema and myocardial fiber disorientation were also apparent (in circle); (g) MTX+*M. oleifera* group showing necrotic centers (arrows) accompanied by severe inflammatory cell infiltration and interstitial edema (in circle); (h) MTX+*A. paniculata* group showing early necrotic signs in the form of focal karyolysis (arrows) with mild inflammatory cell infiltration (H&E staining, 400× magnification). Diabetic groups were induced by STZ-NA injection. H&E=hematoxylin and eosin; IL-6=interleukin-6; LV=left ventricle; MTX=methotrexate; SD=standard deviation; STZ-NA=streptozotocin-nicotinamide. **p*<0.001; †*p* = 0.002; ‡*p* = 0.005

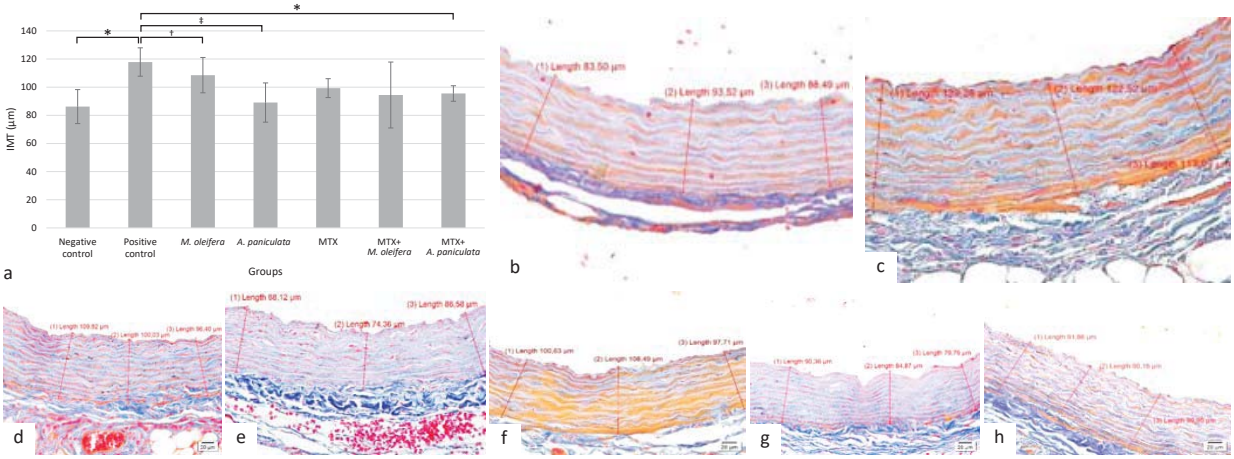

Figure 3. Histopathology of aorta in all groups. The aortic IMT in all experimental groups (mean [SD]) showing significant differences between negative control and positive control, *M. oleifera*, *A. paniculata*, and MTX+*A. paniculata* groups (a); histology of aorta from the negative control (b), positive control (c), *M. oleifera* (d), *A. paniculata* (e), MTX (f), MTX+*M. oleifera* (g), and MTX+*A. paniculata* (h) groups, respectively. Aortic IMT assessments were done by measuring the distance from the endothelial cell layer to the medial-adventitial layers transition zone. The greatest measurement was shown in the positive control group, while the smallest was seen in the negative control group (in µm, Mallory-Azan stain, 400× magnification). Diabetic groups were induced by STZ-NA injection. H&E=hematoxylin and eosin; IMT=intima–media thickness; MTX=methotrexate; SD=standard deviation; STZ-NA=streptozotocin-nicotinamide. **p* = 0.001; †*p* = 0.014; ‡*p* = 0.010

were observed in the myocardium (Figure 2b), whereas these pathological features were observed in the positive control group (Figure 2c). Compared with the positive control group, fewer necrotic centers were observed in the *A. paniculata* and MTX+*A. paniculata* groups, although inflammatory cell infiltration and interstitial edema were still observed. Compared with the *A. paniculata* and MTX+*A. paniculata* groups, the *M. oleifera*, MTX, and MTX+*M. oleifera* groups (Figure 2d–g) showed abundant necrotic centers accompanied

by inflammatory cell infiltration and interstitial edema (Figure 2, e and h).

The aortic IMT measurement results are shown in Figure 3. Compared with the positive control group, the *A. paniculata*, MTX, and MTX+*A. paniculata* groups had significantly thinner IMT.

DISCUSSION

Body weight was increased significantly in the negative control group but decreased in the positive control group. RBG levels significantly increased after STZ-NA hyperglycemia induction with or without MTX, *M. oleifera*, and *A. paniculata* leaf extract treatments. Previous studies have reported that treatment with *M. oleifera* and *A. paniculata* leaf extracts could significantly decrease the blood glucose levels in STZ-NA-induced hyperglycemic animal models.[9,10] In the present study, reduced RBG levels were observed in rats that received either *M. oleifera* or *A. paniculata* extract compared with STZ-NA-induced only. This may be attributed to kaempferol in the leaf extracts of *M. oleifera* and *A. paniculata*.[11] Kaempferol can reduce blood glucose concentration through PI3K and PKC pathways and translocation of GLUT4 in skeletal muscle. Other studies have also shown that *M. oleifera* extract can increase insulin secretion even higher than metformin.[13,26] In these studies, a methanolic compound of *M. oleifera* extract is suggested to have an antioxidant effect in rats with DM induced by a single intraperitoneal injection of STZ (30 mg/kgBW in 0.1 M citrate buffer [pH 4.5]), with significant increases in plasma insulin, activities of glutathione peroxidase, superoxide dismutase, catalase, and glutathione reductase, and decreases in glutathione content, serum glucose, hydroperoxides, glycated hemoglobin, thiobarbituric acid reactive substances, and conjugated dienes.[13,26] Andrographolide lipoic acid can decrease the production of proinflammatory cytokines through the dampening of nuclear factor-κB (NF-κB) pathway, increase insulin secretion, and promote membrane translocation of GLUT4.[10,12] Consistent with previous studies, the present study also showed the hypoglycemic effect of MTX. In another study, MTX had an antihyperglycemic effect in a T1DM animal model.[27]

In the present study, myocardial IL-6 level was significantly increased in the positive control group compared with the negative control group. A previous study reported that hyperglycemia modulates specific epigenetic changes, which would regulate the NF-κB activity and, thus, cytokine expression in vascular cells and cardiomyocytes.[28] Elevated circulating level of IL-6 is an independent biomarker of type 2 DM (T2DM) and is associated with inflammation, beta cell dysfunction, obesity, and insulin resistance; however, other studies have shown a contrasting role of IL-6 as an anti-inflammatory cytokine and a cytokine that can help glucose metabolism.[29–31] In a meta-analysis of 15 prospective studies by Bowker et al,[32] higher IL-6 levels were significantly associated with a higher risk of T2DM incidence. The meta-analysis also revealed that IL-6 levels mediated approximately 5% of T2DM cases and a higher body mass index. Furthermore, the reduced myocardial IL-6 level in animals treated with *M. oleifera* extract may be attributed to the inhibition of NF-κB p65, which in turn reduces the synthesis of subsequent inflammatory mediators, including IL-6 and tumor necrosis factor-alpha (TNF-α).[11,33,34]

The Rocha necrosis score was highest in the MTX+*M. oleifera* group and lowest in the MTX+*A. paniculata* group. The score was significantly lower in the *A. paniculata* group than in the positive control group, possibly due to the potential cardioprotective effect of *A. paniculata* leaf extract on DCM; however, further studies are needed to determine the underlying mechanism. A study by Liang et al[5] showed that andrographolide, one of the components of *A. paniculata* leaf extract, ameliorated DCM in mice by blockage of oxidative damage and inflammation mediated by NF-κB. The cardioprotective effect of andrographolide is due to its capability to restore redox homeostasis by increasing nicotinamide adenine dinucleotide phosphate synthesis in response to hyperglycemia stimulation and the blockage of the messenger RNA expression of several proinflammatory cytokines (TNF-α, IL-1ß, and IL-6).[5]

We observed a significant thickening of the aortic IMT in the positive control group compared with the negative control group. However, decreased IMT was observed in the hyperglycemic groups that received any treatment (*M. oleifera* or *A. paniculata* extracts or MTX, either as a single or combination treatment) compared with the positive control group. Notably, the IMT was more reduced in the MTX group than in the *M. oleifera* group. Furthermore, the IMT was more reduced in the *A. paniculata* group than in the positive control group. Another study reported the effect of andrographolide

in the *A. paniculata* extract as an active compound that inhibits blood vessel thickening in mice exposed to cigarette smoke.[35] This effect was obtained by inhibiting the p38MAPK/HO-NF-kB-ERK2 cascade pathway in platelets. MTX monotherapy can reduce blood vessel thickness, mainly by inhibiting proinflammatory cytokines (especially TNF-α, IL-1, and IL-6), increasing the release of IL-10 as an anti-inflammatory cytokine, inhibiting NF-κB, and activating the 5'-adenosine monophosphate-activated protein kinase pathway that improves nitric oxide balance in endothelial cells.[5] Furthermore, the decrease in IL-6 and TNF-α levels was associated with a significant increase in endothelium-dependent vasodilatation and a reduction in vascular cell adhesion molecule-1. Hypertension and dyslipidemia are the common risk factors observed in patients with T2DM and are associated with the development of atherosclerosis.[36–38] MTX possesses a significant antihyperglycemic effect; however, the administration of this drug as a routine treatment to prevent DCM may not be feasible, considering its side effects, particularly in the myocardial tissue.[39,40] This might have also contributed to the death of a few experimental animals in the present study.

The present study provided data on the potential antihyperglycemic and anti-inflammatory effects of MTX combined with *M. oleifera* and *A. paniculata* leaf extracts on cardiovascular tissues. These combinations exhibited no effect; however, *A. paniculata* leaf extract monotherapy significantly reduced myocardium and aortic wall injuries in the hyperglycemic animal model, whereas *M. oleifera* leaf extract showed promising anti-inflammatory effects on heart tissue. However, further analysis is required. One limitation of this study was that we could not ascertain the specific substances responsible for these findings because we used leaf extracts from whole *M. oleifera* and *A. paniculata* plants. Further study should be conducted to compare the efficacy of the agents used in this study with that of others and the optimum dose for each agent. Therefore, other markers of inflammation and/or myocardial necrosis should be investigated further.

In conclusion, *M. oleifera* leaf extract showed the most beneficial effect in reducing cardiac inflammation, as indicated by decreased IL-6 levels, whereas *A. paniculata* leaf extract showed a greater effect on reducing myocardial injury and aortic wall thickening. In this study, MTX, *M. oleifera,* and *A. paniculata* leaf extracts prevented a decrease in body weight in STZ-NA-induced hyperglycemic rats; however, the antihyperglycemic effect of each treatment was not evident.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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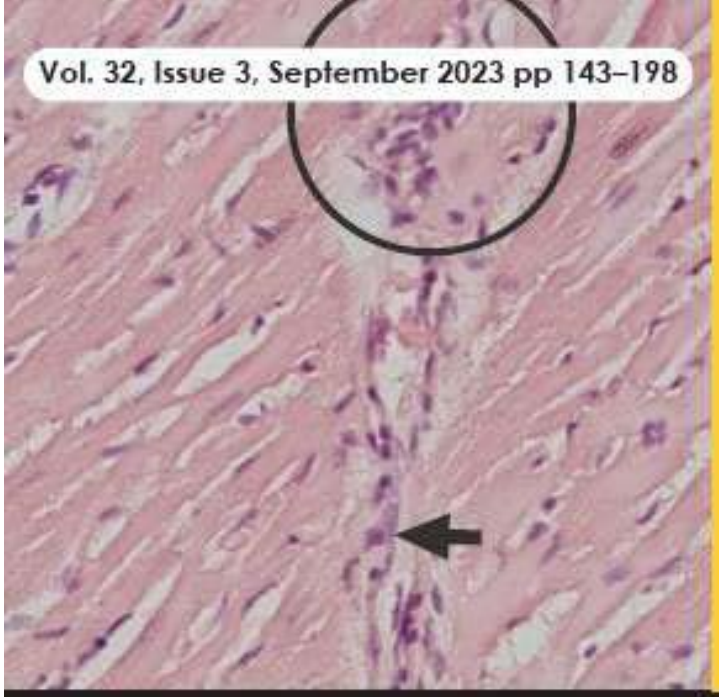

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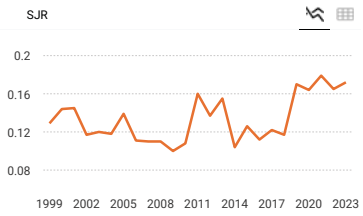

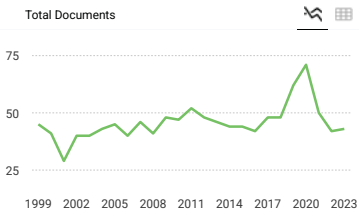

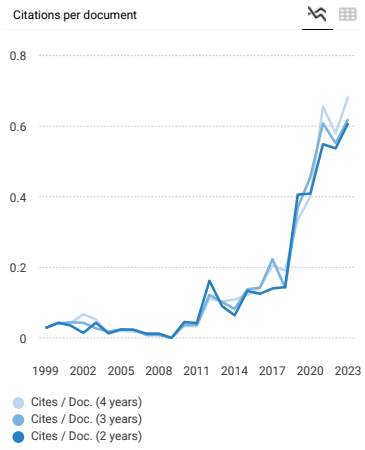

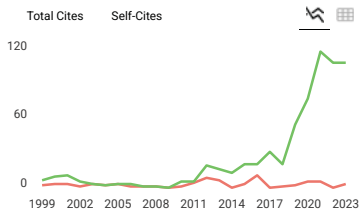

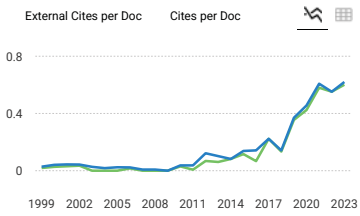

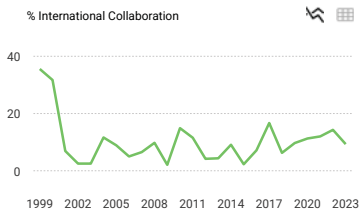

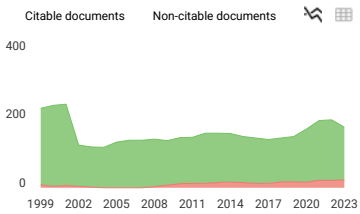

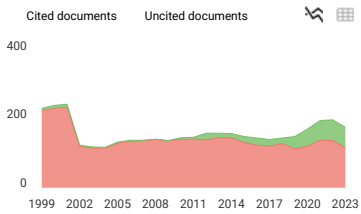

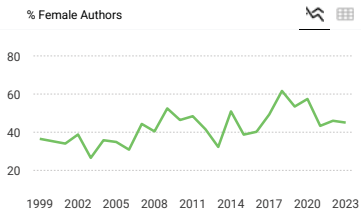

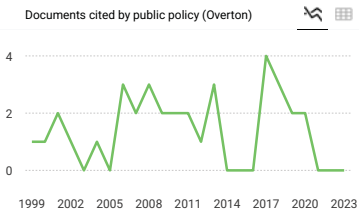

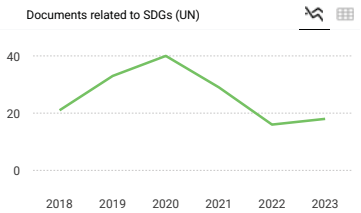

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