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Cardiovascular, Gastric, and Paranasal Effects of Clopidogrel and HMG-CoA Reductase Inhibitors Alone or with Co-medications: An Ultrasonographic and Echocardiographic Study [1]

التأثيرات القلبية، المعدية، وحول الأنفية لمثبطات كلوبيدوغريل و HMG-CoA منفردة أو مع أدوية أخرى: دراسة بالموجات فوق الصوتية وتخطيط صدى القلب [2]

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Abstract: This study aimed to assess the longitudinal myocardial strain of all cardiac walls, evaluate left ventricular function, detect coronary artery deformities and flow disturbances, and analyze indicators of *H. pylori* infection in the stomach and paranasal sinuses. A total of 1,113 male and female patients were examined using echocardiography (B-mode, M-mode, and color Doppler) for cardiac and coronary assessments, alongside ultrasound imaging of the stomach and sinuses, between January 2022 and December 2023, considering the impact of *SARS-CoV-2* variants. Medications included clopidogrel 150 mg, statins 10 mg, aspirin 75 mg, Ginkgo biloba 80 mg, Rumalaya forte, and clarithromycin 250 mg. All patients showed a reduction in at least one longitudinal strain parameter; 95% had normal left ventricular function (EF 65–78%) and 5% had reduced function (EF 25–40%). Coronary deformities appeared as "beaded" narrowings and twists, with gastric fibrous strands linked to *H. pylori* inflammation. High-dose clopidogrel combined with low-dose statins and clarithromycin improved longitudinal strain, left ventricular function, and blood pressure, while reducing the density and spread of fibrous strands within 30 minutes. The study concluded that coronary narrowing improved by 20–30% within the first day, and transthoracic echocardiography with color Doppler provided reliable, early detection of coronary inflammation and collateral involvement. Clarithromycin further supported cardiovascular regulation and reduced *H. pylori*-related lesions, emphasizing the fundamental link between gastric integrity and cardiac health modulated by medications, nutrition, and viral mutations.

Keywords: Clopidogrel 150 mg, statins, clarithromycin, longitudinal myocardial strain, coronary arteries, left ventricular function.

المستخلص: هدفت الدراسة إلى فحص المطاوعة المحورية الطولية لجدران القلب كافة وتقييم وظيفة البطين الأيسر وتشوهات الشرايين التاجية واضطرابات تدفق الدم، إضافة إلى تحليل مؤشرات مرض *H. pylori* في المعدة والجيوب الأنفية. شملت العينة 1113 مريضًا من الجنسين، تم تقييمهم بتخطيط صدى القلب (الوضعان B و Mوالدوبلر اللوني (للقلب والشرايين التاجية، وفحص الموجات فوق الصوتية للمعدة والجيوب الأنفية، خلال الفترة من يناير 2022 إلى ديسمبر 2023 مع مراعاة تأثير متحورات *SARS-CoV-2*. تضمنت العلاجات: كلوبيدوغريل 150 ملغ، الستاتين 10 ملغ، الأسبرين 75 ملغ، جينكوبيلوبا 80 ملغ، رومالايا فورت، وكلاريثروميسين 250 ملغ. أظهرت النتائج انخفاضًا في مقاييس المطاوعة المحورية لدى جميع المرضى، مع وظيفة بطين أيسر طبيعية (EF 65–78%) لدى 95% وضعيفة (EF 25–40%) لدى 5%. وبرزت تشوهات الشرايين التاجية على هيئة عقد خرزية وتضيقات، إضافة إلى خيوط نسيجية معدية مرتبطة بالتهاب الجرثومة الحلزونية. أدى العلاج المشترك بجرعات مرتفعة من كلوبيدوغريل ومنخفضة من الستاتين وكلاريثروميسين إلى تحسين المطاوعة المحورية ووظيفة البطين الأيسر وخفض ضغط الدم وتقليل كثافة الخيوط النسيجية خلال 30 دقيقة. خلصت الدراسة إلى تحسن مناطق التضيق التاجي بنسبة 20–30% في اليوم الأول، وإثبات فعالية تخطيط الصدى والدوبلر كوسيلتين مبكرتين للتشخيص والمتابعة، إضافة إلى دور الكلاريثروميسين في تنظيم الوظائف القلبية والوعائية وخفض تأثيرات الجرثومة الحلزونية والالتهابات المصاحبة لمتحورات *SARS-CoV-2*. وتؤكد النتائج الترابط الحيوي بين صحة المعدة وسلامة القلب استجابةً لتأثيرات الأدوية والأغذية وتغيرات الفيروسات.

الكلمات المفتاحية: كلوبيدوغريل 150 ملغ، الستاتين، كلاريثروميسين، المطاوعة المحورية القلبية، الشرايين التاجية، وظيفة البطين الأيسر.

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2-**الاقتباس (APA7)**: الأشول، نشوان صالح محمد. (2025). التأثيرات القلبية، المعدية، وحول الأنفية لمثبطات كلوبيدوغريل و HMG-CoA منفردة أو مع أدوية أخرى: دراسة بالموجات فوق الصوتية وتخطيط صدى القلب. ***مجلة مركز الجزيرة العربية للبحوث الطبية والتطبيقية، 1***(3)، 51–75. https://doi.org/10.56793/pcra23133

1-Introduction.

Cardiovascular diseases, coronary artery stenosis, and **Helicobacter pylori** (H. pylori) infections have markedly increased worldwide, contributing to morbidity and mortality, mainly through atherosclerosis [1]. H. pylori also causes various gastric and extra-gastric disorders [2]. Delayed or misdiagnosed cases can lead to progressive cardiac tissue damage, especially when gastrointestinal, musculoskeletal, neurological, and cardiac symptoms overlap, as seen in H. pylori-induced systemic inflammation, including paranasal sinus thread-like mucosal hypertrophy.

It is hypothesized that persistent gastric H. pylori inflammation spreads systemically via pro-inflammatory cytokines and may be exacerbated by viral agents like SARS-CoV-2 and its variants. Therefore, developing accurate, cost-effective, non-invasive diagnostics for early detection and therapeutic adjustment is crucial.

This study introduces an integrated approach using echocardiography (B- and M-mode, color Doppler) to assess cardiac long-axis motion, LV function, and coronary artery morphology, combined with abdominal ultrasonography to detect thread-like inflammatory tissue in gastric and paranasal regions. Comparative assessments were performed pre- and 30 minutes post-drug intervention, with additional clinical evaluation within 15–30 minutes to capture both therapeutic and adverse effects.

Changes in echocardiographic parameters—ejection and shortening fractions, cardiac dimensions, and vascular amplitudes—were correlated with ultrasonographic findings to evaluate systemic inflammation and drug efficacy. Dynamic variations may also indicate emerging SARS-CoV-2 variants, providing a rapid alternative to genomic sequencing, with potential applications in other therapeutic fields, such as oncology, where drug administration routes influence patient outcomes.

1-2-Problem Statement:

Although H. pylori infection and cardiovascular disorders are among the most prevalent global health challenges, diagnostic methods often fail to identify overlapping pathologies in their early stages. The delayed recognition of H. pylori-induced systemic inflammation —particularly its cardiac manifestations — contributes to mismanagement and increased morbidity. Moreover, the reactivation of these inflammatory processes by SARS-CoV-2 variants further complicates diagnosis and treatment. Therefore, the current challenge lies in developing an affordable, accurate, and rapid diagnostic method capable of detecting inflammatory and pharmacologic changes across gastric and cardiac systems simultaneously.

1-3-Research Questions:

1. How do these drugs exert rapid, systemic effects on cardiac and vascular function before being metabolized?
2. Is there a pathological link between chronic **H. pylori** infection and the development of extra-gastric diseases like **atherosclerosis** and **fibromuscular dysplasia**?
3. How have **SARS-CoV-2** and its variants altered the efficacy of conventional drugs by modulating the host inflammatory response?

1-4-Research Objectives:

1. To investigate the mechanism by which drug particles, upon contact with the gastric mucosa, induce cytokine production that leads to rapid systemic improvements.
2. To determine if **H. pylori** infection contributes to systemic vascular diseases by comparing inflammatory cytokine profiles in infected patients with those suffering from vascular disease.

3. To evaluate the shifts in drug efficacy and their effects on specific inflammatory pathways in patients exposed to different **SARS-CoV-2** variants.

1-5- Research Significance:

This research contributes to both theoretical knowledge and practical clinical applications:

- **Theoretical Significance:**

– This study challenges the conventional understanding of pharmacodynamics by proposing a novel, non-metabolic mechanism for rapid drug action, initiated directly from the gastric mucosa.

– It introduces a new hypothesis linking **H. pylori** infection to the etiology of systemic vascular diseases, particularly **atherosclerosis** and **fibromuscular dysplasia**, via a shared inflammatory pathway.

- **Practical and Applied Significance:**

– The research highlights the immense value of simple, cost-effective, and non-invasive diagnostic tools like echocardiography and ultrasonography for the early detection and management of a wide range of diseases.

– It provides a new framework for personalized medicine, underscoring the necessity of continuously adapting drug regimens in response to evolving viral variants and their impact on host immunity.

– The findings suggest a novel therapeutic approach that focuses on regulating the core inflammatory pathways (**TLR4, NF-ΚB, etc.**) rather than merely managing symptoms.

– The study's observations on the potential for drugs to have negative or paradoxical effects depending on the patient's immune state underscore the critical need for a vigilant and dynamic approach to patient care and drug administration.

– This work advocates for a shift in focus from lipid disorders as the primary cause of vascular disease to the underlying inflammatory process, which is often a more viable therapeutic target.

1-6-Limitations of the Research:

The study's observational design limit causal inferences. Molecular mechanism conclusions are based on clinical observations rather than direct data, and multiple drug combinations complicate effect attribution. Findings' generalizability is also limited by the 2022–2023 study period, as drug responses may change with emerging viral variants

2-Methods and Materials.

2.1 Study Design:

This research employed an observational, cross-sectional design using a random sampling approach. The study was conducted to evaluate the physiological and pharmacological effects of selected drug regimens on cardiac and gastric parameters through non-invasive imaging modalities. The design allowed for clinical observation of patient responses before and after drug administration without intervention bias.

2.2 Study Population and Sampling:

A total of 1,113 patients (500 females, 44.9%; 613 males, 55.1%) participated in the study. All were patients attending Dr. Nashwan Al-Ashwal Clinic for Medical and Cardiac Diseases, located in Adhale Governorate, Republic of Yemen, between January 1, 2022, and December 31, 2023. Participants were randomly enrolled during routine clinic visits, ensuring a

representative distribution of age and sex. Patients with severe cardiac failure, malignancy, or incomplete records were excluded to maintain data consistency.

2.3 Research Tools and Data Collection

The primary diagnostic tools included transthoracic echocardiography (B- and M-modes and color Doppler) and abdominal ultrasonography for gastric and paranasal sinus evaluations.

Echocardiographic assessment: The M-line was positioned on the mitral annulus (lateral, septal, anterior, inferior, and posterior LV walls) and the tricuspid annulus of the right ventricle. Coronary arteries were visualized using a sector probe in either cardiac or abdominal mode (the latter preferred), with optimized parameters for clarity (scale, frequency 3.0, persistence 3–4, filter adjustments).

Ultrasonographic assessment: Gastric tissues were imaged in mid-epigastric long and short views after ingestion of approximately 350 mL of water, or through a left lateral oblique view. Maxillary sinuses were examined via long and short views below the maxillary prominence. Patients were divided into two groups:

Group A (Treated): n = 556 (250 females, 306 males). **Group B (Control)**: n = 557 (250 females, 307 males).

Group A received the therapeutic regimen first, and after evaluation, the same protocol was applied to Group B for comparative observation. Clinical improvement, along with positive echocardiographic or ultrasonographic findings, was considered a positive drug effect, whereas deterioration in any clinical or imaging parameter was recorded as a negative effect, prompting discontinuation of the related medication.

The therapeutic combinations are detailed in Table (1), where drugs with positive responses were retained and those with negative effects were discontinued.

2.4 Validity and Reliability:

To ensure instrument validity, all echocardiographic and ultrasonographic examinations were performed by the same physician using standardized imaging protocols. Device calibration was verified weekly, and duplicate readings were obtained for 10% of patients to assess measurement reliability, achieving a consistency rate above 0.92 (Cronbach's α). Clinical interpretations were independently reviewed by a second cardiologist to minimize observer bias.

2.5 Data Analysis:

Data were compiled and coded in Microsoft Excel 2021, with descriptive statistics (mean, SD, frequency) and comparative assessments of pre- and post-treatment imaging findings. Temporal drug effects were tracked per quarter between 2022 and 2023, according to Table (1).

2.6 Ethical Considerations:

All procedures complied with the Declaration of Helsinki (2013). Written informed consent was obtained, and patient confidentiality was ensured by anonymizing identifiers. Drug regimens were tailored to individual responses (Table 1), and all clinical and imaging data were recorded and analyzed using Microsoft Excel.

Table (1): represent drugs regime for patients in the periods of study from January 2022 to December 2023

Drugs	Year 2022								Year 2023					
	Jan 01 – 30	17/June- -/Aug30	31/Aug- /Oct16	Oct 17 - 27	28/Oct - 31/ Dec	01/Jan –16/ June	June 17-20	June 21-24	25/June –15/ July	July 16 - 31	01/Aug – 24/Oct	25/Oct –05/ Nov	Nov 06 - 30	Dec 01 - 31
Clopidogrel tab150mg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
Aspirin tab	x	✓	x	x	x	x	x	x	x	x	x	✓	x	x

75 mg														
Ator tab 10 mg	✓	✓	✓	✓	✓	✓	x	✓	x	✓	x	x	x	x
Rosu tab 10 mg	x	x	x	x	x	x	✓	x	x	x	x	✓	x	x
Simva +Ezet tab 10 +10mg	x	x	x	x	x	x	x	x	✓	x	x	x	x	✓
Ator +Rosu tab 10 +10 mg	x	x	x	x	x	x	x	x	x	x	✓	x	x	x
Rumalaya forte tab	x	x	x	x	x	x	x	x	x	x	x	x	✓	x
Ginkgobiloba/cap80mg	x	x	x	x	x	x	x	x	x	x	x	x	✓	x
Clarithromycin tab 250 mg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X 23-26 August	✓	✓	✓

Ator = Atorvastatin. Rosu = Rosuvastatin. Simva = Simvastatin. Ezet = Ezetimibe.

4-The Results.

Pre-therapeutic period:

1. **Long-axis amplitudes and left ventricular (LV) function:** Measurements showed amplitudes ranging from **4.6–13 mm** (Types I–IV and VI) and above **13 mm** up to 23 mm. As presented in Table (2), **95% of patients (n = 1057)** had normal LV function (EF 65–78%), whereas **5% (n = 56)** exhibited impaired function (EF 25–40%). Patterns of deterioration included:
   - **Type I (56%)**: Reduced lateral and septal axes (<11 mm), others normal.
   - **Type II (13%)**: Reduced anterior axis (<10 mm).
   - **Type III (11%)**: Four axes affected (lateral, septal, anterior, inferior).
   - **Type IV (8%)**: Severely reduced lateral axis (6.5 mm) with hyperkinetic anterior (16.8 mm) and inferior (18.7 mm); associated with acute palpitations and dyspnea.
   - **Type V (7%)**: Involvement of one LV and one RV axis; patients presented with recurrent dyspnea and predominant back pain.
   - **Type VI (5%)**: All axes deteriorated (<7 mm), enlarged LV dimensions, and severe dysfunction (EF ≤25%, FS ≤12%).

Table (2) represents long axes amplitudes of cardiac walls, left ventricular functions and types of axes deterioration according to their presentation

Long axes and left ventricle function	Types* and values of presented long axes amplitudes					
	I (56%)	II (13%)	III (11%)	IV (8%)	V (7%)	VI (5%)
Lateral	10.9	13.8	10.4	06.5	14.7	04.6
Septal	10.9	14.9	09.4	10.3	12.9	06.5
Anterior	11.9	09.8	09.4	16.8	12.9	04.6
Inferior	11.4	13.8	10.9	18.7	13.3	04.6
Posterior	14.4	12.1	12.4	11.5	10.6	05.9
Right Ventricle	20.4	21.2	22.4	23.3	19.3	05.2
LVED	55.2	48.8	40.3	42.8	59.2	70.9
LVES	34.3	30.4	21.9	27.5	34.9	62.4
EF%	67%	68%	78%	65%	71%	25%
FS%	38%	38%	46%	36%	41%	12%

Coronary arteries: Ultrasonography and color Doppler imaging demonstrated extensive arterial networks with elongated tortuous vessels, "string-of-beads" appearance, and stenosis affecting even small branches (Figure 1). Large colored coronary networks were observed in patients with preserved EF (Figures 2A, B, G, H), whereas reduced vessel density and severe narrowing predominated in those with lowest EF (Figures 2C, F; Figure 13). Additional findings included tubular and atheromatous-like stenoses with string-of-beads patterns in smaller vessels (Figure 3), and newly formed collateral vessels appearing blue and narrowed, indicating active inflammatory processes (Figure 4, white arrows)

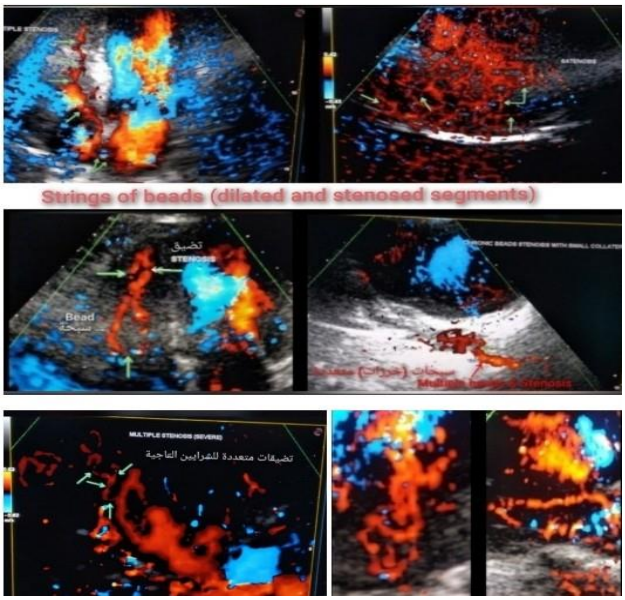


Figure 1: strings of beads along the coronary arteries, a result of dilated and stenotic regions along the arterial lengths, and leads to chest or back pain and/or shortness of breathing with exercise due to the slow flowing of blood as a result of the multiple and sequenced stenosis.

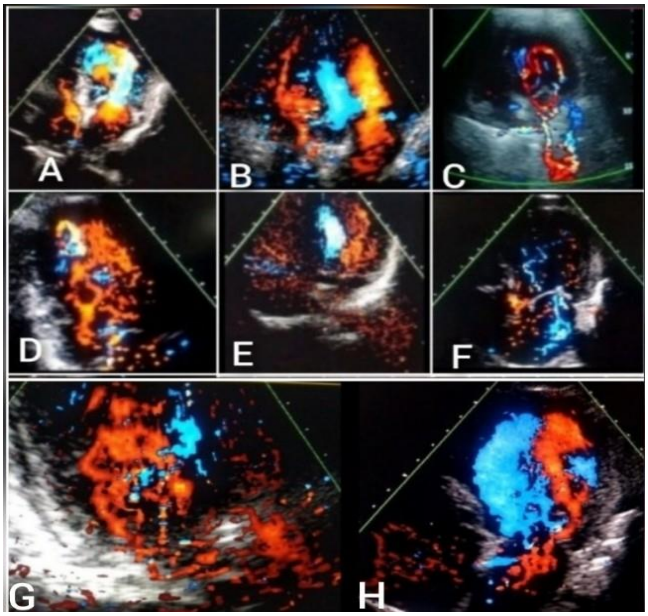
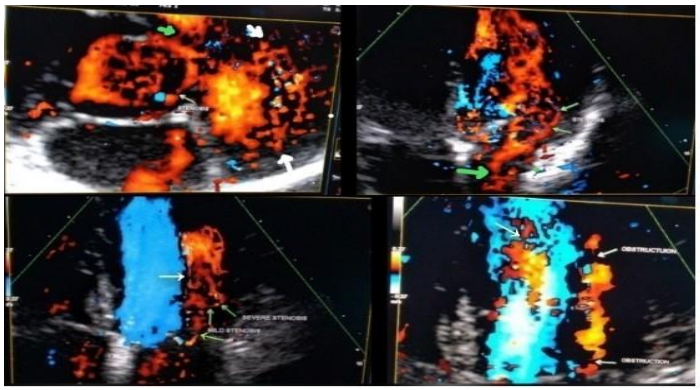


Figure 2 illustrates coronary arteries with long-axis amplitudes of 13–9.5 mm and normal ejection/shortening fractions (A, B, D–H). Amplitudes below 9 mm (C) correspond to reduced LV function. Progressive coronary network decline leads to ventricular dysfunction, with mosaic color showing an upper obstruction and a lower segment connecting red zones."



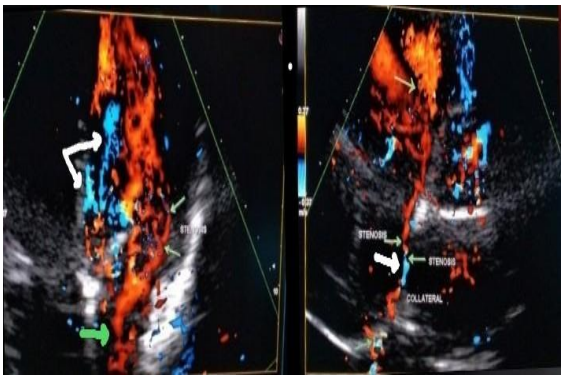


figure 3 presents cardiac views showing different coronary stenoses: beads, string-like stenosis (white arrows), focal hypertrophy-related stenosis (large green arrow), and unilateral wall hypertrophy stenosis (thin green arrow). Atheroma-like projections and complete vessel obliteration are also visible, with light green arrows indicating stenotic areas appearing as black gaps between vessel ends

Figure 4: shows main branch stenosis (large green arrow) and blue collateral segments in between red arteries (white arrows), the photo in right side reveals stenotic one end of this blue collateral vascular segment which means that the inflammatory process involved even the collateral vessels, and also will involve the transplanted one

3- in relation to Tissues threads of gastric and maxillary paranasal sinuses: there are a lot of tissues threads that lead to formation of complex networks or masses as shown in figures (5 &6)

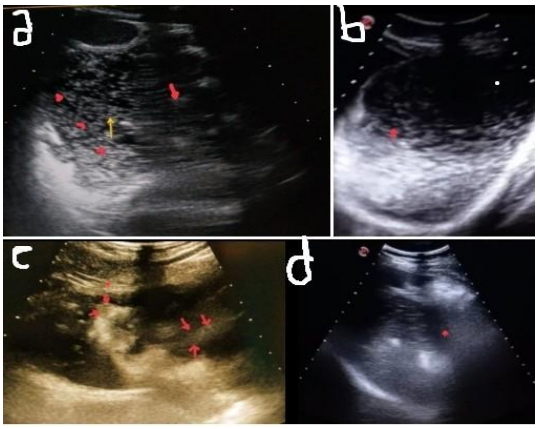


figure 5: gastric threads and mass with Eye – sign (pointing to it by yellow arrow in photo (a), and red arrows and arrows heads in all photos a - d), *that considered by me; in previous study, as pathognomonic sign for H. pylori diagnosis by ultrasonogram and other radiological methods.*

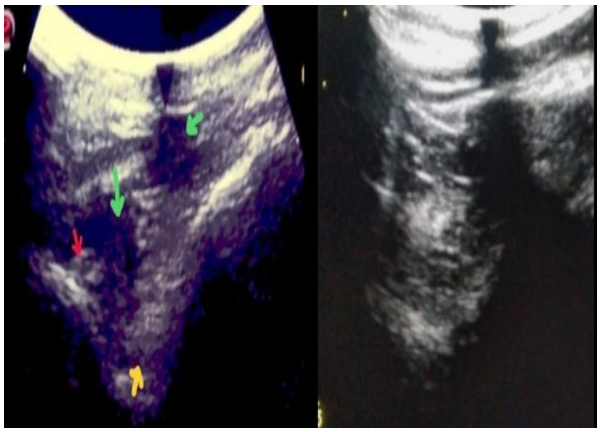


Figure 6*:* Ultrasonography of the maxillary paranasal sinuses shows tissue threads (green arrows), the radiological pathognomonic "Eye Sign" of *H. pylori* (red arrow), and thread aggregation forming a mass (yellow arrow) in the left image, while the right image depicts the sinus cavity filled with a dense mass of clustered tissue threads.

2) Post-Therapy Findings.

1. Effects of Drugs on Clinical Manifestations, Long-Axis Amplitudes, LV Function, and Coronary Arteries

A. Effects on Clinical Manifestations

- **Symptoms:** Chest, back, and shoulder pain, as well as dyspnea, subsided within 30 minutes in *Group A* following drug intake. No improvement was observed in *Group B* until therapy was initiated, after which their results paralleled *Group A*.
- **Blood Pressure:**
- **Positive effects:** Hypertension decreased by **20/10–30/20 mmHg** within 15–30 minutes after two *Clopidogrel* tablets. And A reduction of **20/10 mmHg** was achieved after 20–30 minutes of *Atorvastatin (10 mg), Simvastatin (10 mg), Ginkgo biloba (80 mg),* or *Clarithromycin (250 mg)*. Hypotension improved by **+10–20/10 mmHg** within 30 minutes after *Clopidogrel* (2 tabs) or *Clarithromycin* (250 mg).
- **Negative effects:** A rebound increase of **+20/10 mmHg** occurred in both hypertensive and hypotensive patients within 30 minutes of single-drug use.

- **Heart Rate and Pulse Volume:** Heart rate declined from **57 ⟶ 37 bpm** in a 70-year-old female after *Clopidogrel (150 mg)* (negative effect). And A mild decline (**61 ⟶ 57 bpm**) occurred with *Aspirin (75 mg)* (positive effect). • *Simvastatin*, *Atorvastatin*, or *Clarithromycin* increased heart rate and pulse volume, rendering weak pulses palpable. • Combined regimens sustained improvement, while single-drug use produced temporary effects.
- **Adverse Effects:** Some drugs caused temporary adverse effects—abdominal bloating, headache, hypertension, metabolic disturbances (glucose, lipids, creatinine), joint pain, bradycardia, limb numbness, or impotence—often accompanied by pathological echocardiographic and ultrasonographic changes.

B. Effects on Long-Axis Amplitudes and Left Ventricular (LV) Function:

- **Group A (Treated):** All patients exhibited symptomatic improvement with increased long-axis amplitudes and enhanced LV function (Tables 2 & 3).
- *Type V* showed exceptions—amplitudes and LV function declined after *Clopidogrel (75 mg)* and *Atorvastatin (10 mg)* (ejection fraction **71% ⟶ 57%**, shortening fraction **41% ⟶ 30%**)
- Function and amplitudes normalized after *Ginkgo biloba (80 mg)* and half *Rumalaya Forte* tablet, leading to:
  - Restoration of LV function and amplitudes (Tables 2 & 3).
  - Expansion of coronary network extension (Figures 7, 9, 14–16, 19, 24).
  - Elongation and widening of major coronary arteries (Figures 13, 18–21).
- **Group B (Control):** No changes were observed after 30–60 minutes. Improvement occurred only after therapy, matching *Group A* outcomes

Table (3): represents changes in long axes amplitudes of walls of left and right ventricles &left ventricular function after 30 minutes of drugs intake

Long axes and left ventricle function	Improvements after 30 minutes of taking drugs (for cases in table 2)					
	I (56%)	II (13%)	III (11%)	IV (8%)	V (7%)	VI (5%)
Lateral	16.1	12.4	11.9	11.4	15.6	05.7
Septal	10.9	13.4	11.4	13.9	09.8	04.6
Anterior	14.9	14.9	13.4	12.3	13.0	07.5
Inferior	11.5	12.9	12.4	13.9	11.1	05.2
Posterior	14.9	12.4	14.4	12.3	24.1	08.0
Right ventricle	23.5	18.4	19.9	19.6	24.1	08.6
LVED	50.2	50.7	48.2	49.4	62.3	75.7
LVES	30.3	26.0	24.4	31.4	43.3	61.4
EF%	70%	78%	81%	68%	57%	38%
SF%	40%	47%	49%	38%	30%	19%

C) Relation between Long Axes and Coronary Artery Networks Before and After 30 Minutes of Therapy:

In 95% of patients from both groups, drug intake led within 30 minutes to increased long-axis amplitudes and extension of coronary artery networks (Figures 7–12). In 5% of patients, partial improvements were observed, with enhanced amplitudes in some walls and enlarged vascular networks (Figure 12), while other axes showed reduced amplitudes associated with diminished network areas, decreased color flow, and limited collateral formation (Figure 1E–F; Figures 17, 22, 23). Overall, changes in long-axis amplitudes were directly correlated with coronary network expansion and elongation of major arteries.

1) Lateral & Septal long axes amplitudes and coronary arteries networks areas of both walls

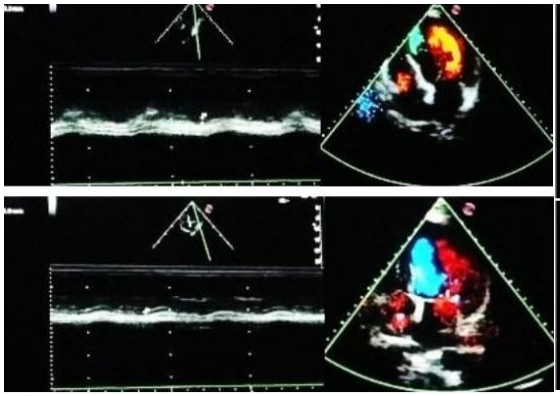


Figure 7: Lateral wall axis and coronary arteries—upper images (pre-therapy) show a lateral long-axis amplitude of 10.3 mm with visible coronary vessels, while lower images (post-therapy) reveal a reduced lateral axis amplitude of 8.8 mm. The coronary vessels along the lateral wall appear decreased post-therapy, whereas septal vessels and septal axis amplitude show a noticeable increase.

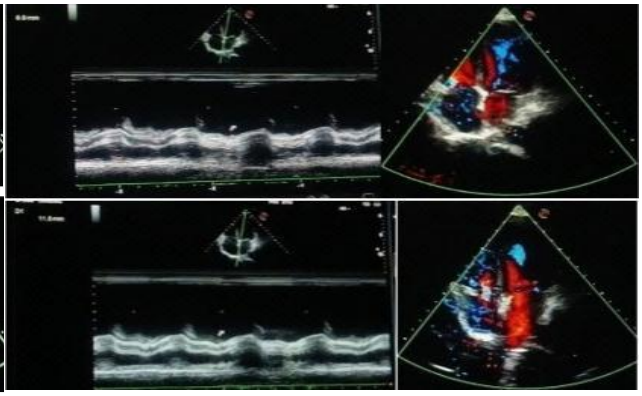


Figure 8: Septal long axis in upper photo is 6.3 mm as it was measured in pre therapeutic period, and its coronary vessels is shown in the photo beside it, and the lower photos taken in post therapeutic period; the septal long axis is 8.9 mm that mean increased in height by 2.6 mm, and the coronary vessels (red color) in right side become more elongated and wider.

3) Anterior, Inferior, posterior and RV long axes amplitudes and coronary arteries networks areas of these wall:

1) Anterior long axis amplitude and coronary arteries networks areas of anterior wall:

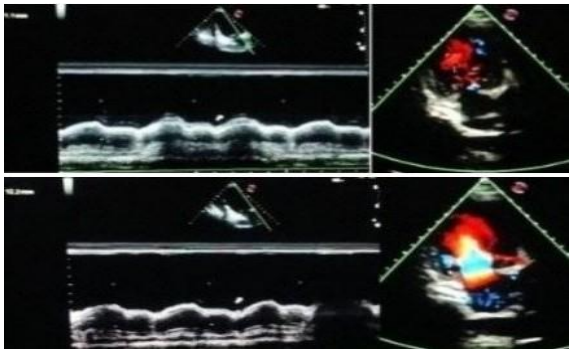


Figure 9: Anterior long axis amplitude in pre therapeutic period is 11.1 mm as shown in left upper photo, and its coronary arteries is shown in right upper photo, while the lower photos are show anterior long axis amplitude height is 12.2 mm in post therapy period after 30 minutes with enlarged extension of coronary arteries as shown in lower right photo.

2) Inferior long axis and coronary arteries networks areas of inferior wall:

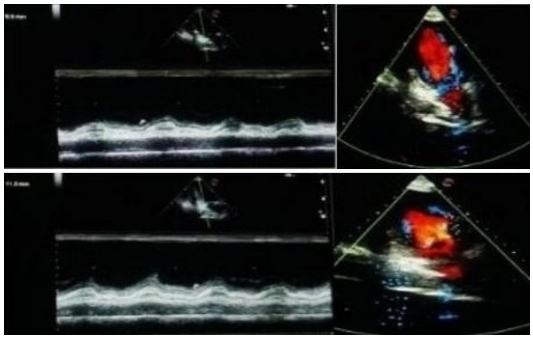


Figure 10: Long axis of the inferior wall and its coronary vessels—upper images (pre-therapy) show an amplitude of 9.9 mm with visible coronary extension, while lower images (30 minutes post-therapy) reveal an increased amplitude of 11.5 mm and an enlarged coronary vessel area, indicating improved perfusion.

3) Posterior long axis amplitude and coronary arteries networks areas of posterior wall:

4) Right ventricular long axis amplitude and coronary arteries networks areas of its wall:

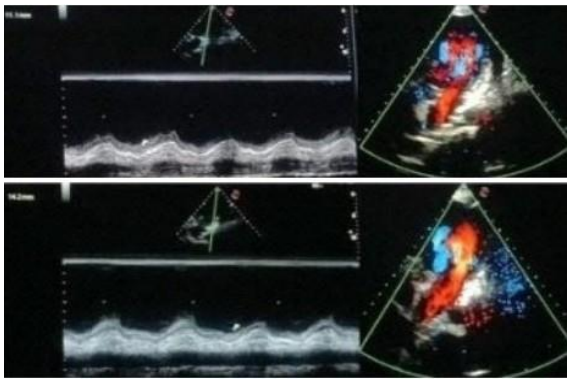


Figure 11: Posterior long-axis amplitudes and coronary arteries pre- and 30-minutes post-therapy. In the upper images, the long-axis amplitude is 11.1 mm (left) with coronary artery extension (right) during the pre-therapy period. In the lower images, post-therapy, the posterior long-axis amplitude increases to 14.2 mm, with enlarged coronary vascular extension (colored areas).

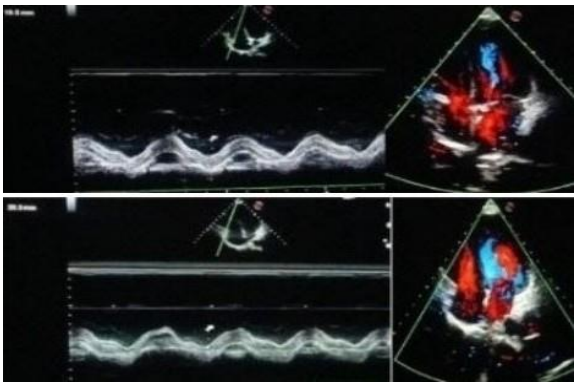


Figure 12: Right ventricular long-axis amplitude and coronary vessels pre- and 30 minutes post-therapy. The upper left image shows a 19.5 mm axis with right coronary artery extension pre-therapy. The lower left image shows post-therapy changes, with the axis increased to 20.1 mm and enlargement of the right coronary vascular area, as seen in the lower right image.

D- Effects on coronary arteries areas extension by comparing between their shapes and color extension:

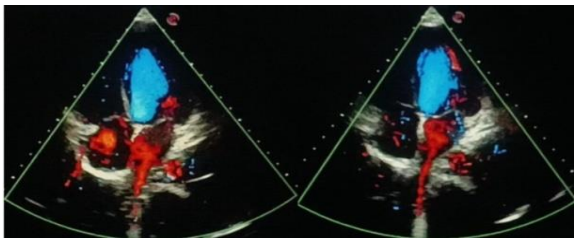


Figure 13: Elongation of coronary artery and visualization of distal beads after 30 minutes of therapy, as seen in right photo, that not visualized in pretherapeutic period as seen in leftt photo

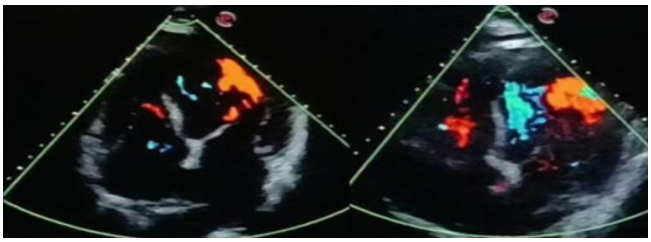


Figure 14: Dilated cardiomyopathy with reduced ejection fraction. The left (pre-therapy) image shows narrow septal and lateral coronary zones, while the right (post-therapy) image displays enlarged vessels and fine red strands forming a "string-of-beads" pattern near the mitral leaflets between red and blue flows

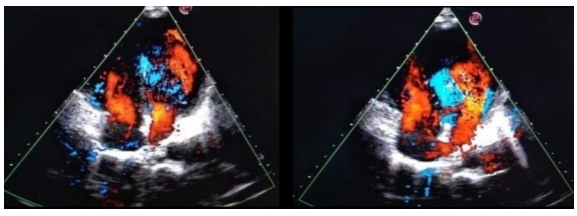


Figure 15: The left image shows left ventricular coronary arteries with two red zones linked by small vessels and scattered blue areas. The right (post-therapy) image displays well-developed arterial networks, merged blue zones, and renewed left–right coronary connections at ventricular and atrial levels, with an elongated, widened right ventricular red area

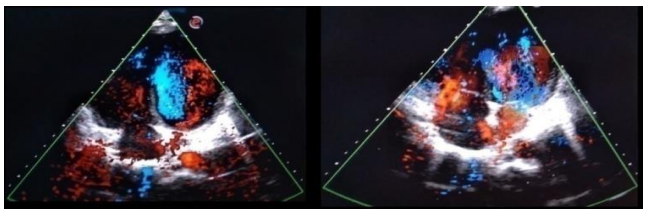


Figure 16: A clear contrast is seen between the left and right images. After 30 minutes of drug intake, coronary arteries reappear, with more distinct red and blue arterial networks in the left ventricle and larger red zones with extending vessels in the right ventricle compared to the pre-therapy image.

E- Effects on longer coronary arteries width and length:

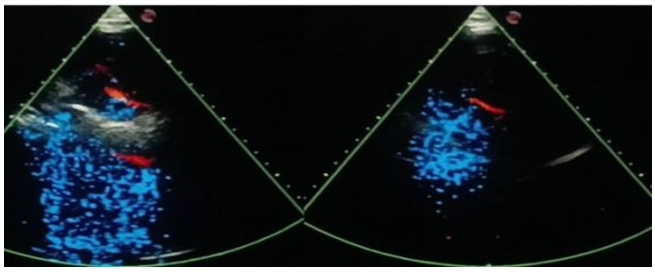


Figure 12: left side photo in pre therapeutic period reveals coronary vessels with red and blue colors more than right photo that reveals a reduction in length, width and number of red coronary arteries after drugs intake of ginkgo biloba tab while it return to pre therapeutic period after intake of ginkgo biloba capsule.

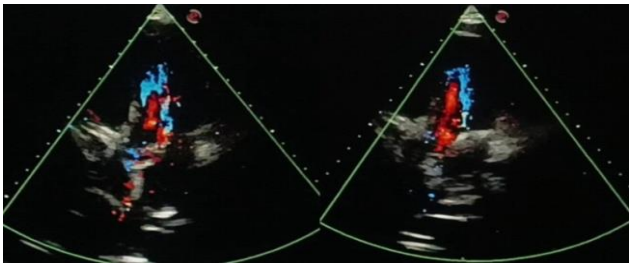


Figure 18: Five-chamber view of coronary arteries—left image (pre-therapy) shows short red and blue vessels along the septal wall, while the right image (30 minutes post-therapy) demonstrates increased vessel length and width, disappearance of the distal mosaic segment, and elongation with narrowing of the proximal mosaic segment near the mitral leaflet.

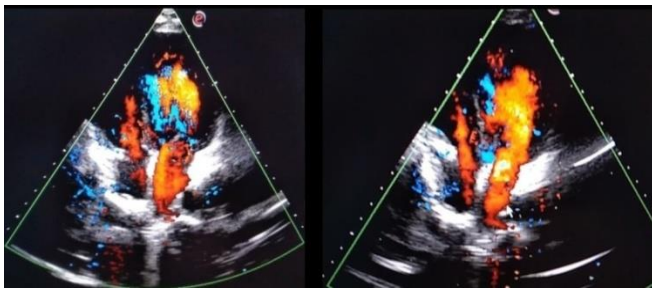


Figure 19: Comparison of pre- and post-therapy images—left image shows a stenosed, shortened right coronary artery, while the right image (30 minutes post-therapy) reveals a longer, wider vessel. The left coronary network (red areas in the atrium and ventricle) displays interrupted gaps pre-therapy that are restored post-therapy through reconnected and newly formed vascular networks.

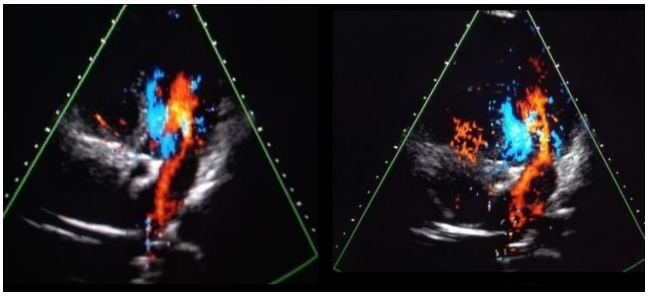


Figure 20: 5 chambers view, it shows narrowing of branch of left coronary artery in left photo; red color, size 2.1 mm at stenosed site, while it becomes wider; size 5 mm, in right photo after 30 minutes of drugs intake, along with re-emerging of right ventricular CAs multiple short branches, and reducing the hyperechogenic reflection (i.e. reducing fibrosis echogenicity)

F- Effects of drug/drugs on blood flowing in systolic and diastolic phases of Coronary arteries

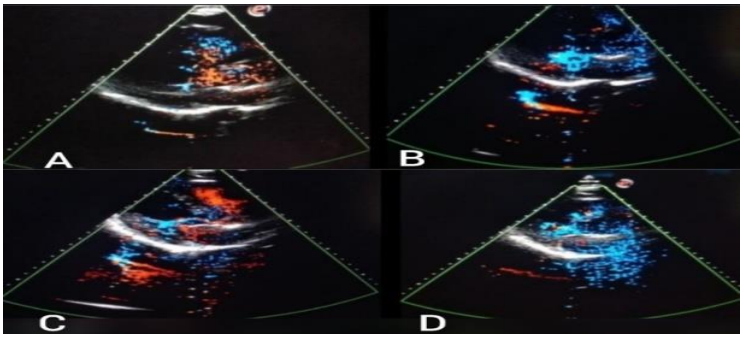


Figure 21: Diastolic (A, C) and systolic (B, D) phases. Pre-therapy, the posterior descending coronary artery is narrow in diastole (A) and wider in systole (B). After 30 minutes of drug intake, it widens with increased red coronary branches in diastole (C), while in systole (D) the artery becomes thinner and red branches of the posterior descending artery disappear.

G- **The negative effects of drugs on coronary arteries**

Reduction in CAs numbers and width or calibers as shown in these figures (22, 23 & 24).

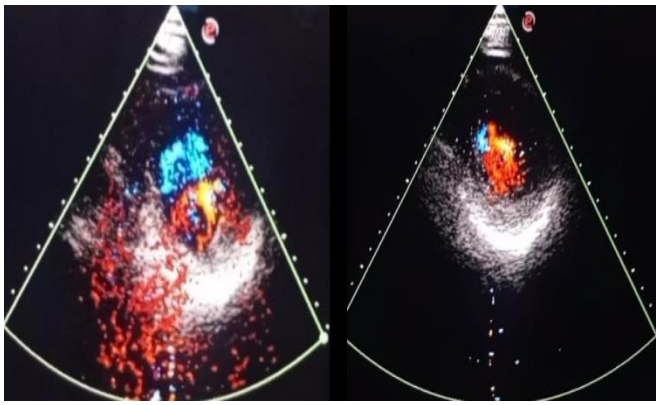


Figure 22: Comparison of right and left images shows markedly reduced coronary color areas in the lower LV cavity, with absent vessels in both epicardial and myocardial regions—findings attributed to vasoconstriction induced by Ginkgo biloba tablets, despite their otherwise positive systemic effects at the time.

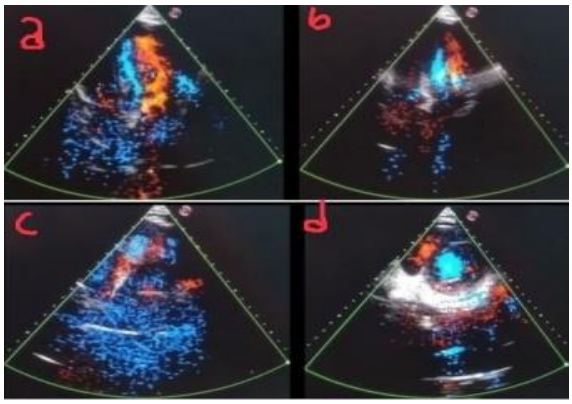


Figure 23: shows reduction in coronary arteries network areas and collateral vessels in the b & d photos after30 minutes of Rosuvastatin 10 and 20 mg during its negative period.

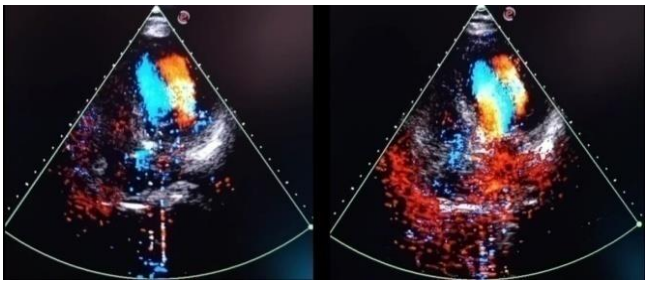


Figure 24: Coronary arteries in patients on Aspirin 75 mg and Atorvastatin 20 mg for one month (left image) and vascular changes 30 minutes after two clopidogrel 75 mg tablets (150 mg) intake. During this period, with positive Aspirin effects and transient clopidogrel effects, collateral vessels were reduced in the left image but increased in the right image.

2-Effects of drugs on Maxillary Para-Nasal Sinuses and gastric tissues threads.

A) **Gastric Tissues Threads:**

1-after 30 minutes of drugs intake there was a reduction in their extension and echogenicity during drugs positive effects as shown in figure (25)

2-After hours of drugs ingestion, patients felt burning sensation in epigastric; xiphoidal region and expel bloody fluid with masses as seen in figure (26).

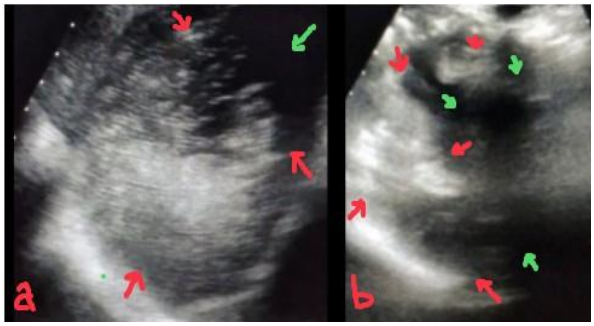


Figure 25: (a) shows gastric tissues threads mass (red arrows) and small area of anechogenic reflection; black color; i.e. water

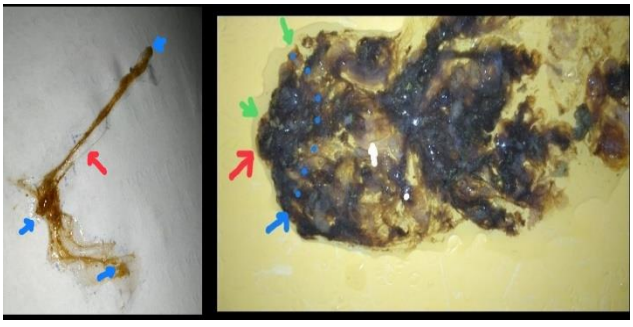


Figure 26: Gastric tissue threads — left image shows a single thread (red arrow) with a nodus branching into multiple fibers (blue arrows), forming a

(green arrow) in left photo before drugs intake and reduction in mass of tissues threads (red arrows), with enlarging of black color (water area) as pointing to it by (green arrows) in right photo (b) after 30 minutes of drugs intake.

tissue skeleton vomited 8 hours after sildenafil with pepper, clopidogrel, and atorvastatin. Right image, 4 hours after multiple drugs, shows a large tissue mass (red arrow) covered by jelly-like mucus (green arrow) with smaller branching threads (blue arrows), partially adhering for over three days with extensions visible through the mucus

B)Maxillary Paranasal sinuses Tissues Threads:

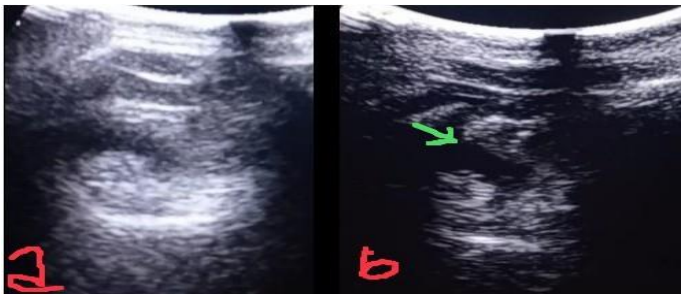


Figure27: (a) shows maxillary paranasal sinuse tissues threads with hyperechogenic reflection in left photo before drug intakes and positive effect that leads to reduction in echogenicity (brightness) and increase in black space (green arrow) after 30 minutes of drug intake as seen in right photo (b).

3- Negative Effects Of Drugs on Tissues Threads of Gastric And Maxillary Paranasal Sinuses.

The negative effects of drugs lead to enhancement of echogenicity and stimulation of tissues threads formation, extension and thickening to the degree of mass formation and obliteration of spaces, as shown down

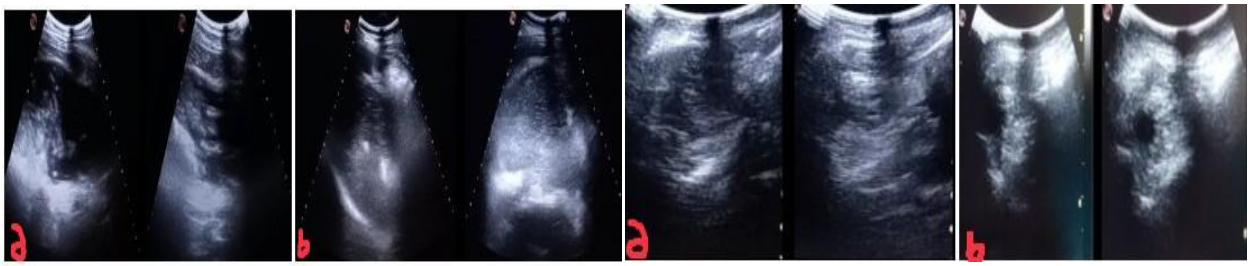


Figure 28: Gastric tissue threads before and 30 minutes after drug intake. The left image shows thickened threads and reduced dark fluid after clopidogrel, indicating tissue extension, while the right image shows thinner threads and an expanded dark area, reflecting rosuvastatin's negative effect

Figure 29: shows maxillary sinuses with negative effects (increasing of echogenicity and tissues threads extension after 30 minutes of drugs intake; (a) after ginkgo biloba tabs, and (b) after rumalaya forte tab.

Table (4) represent drugs effects on blood pressure, heart rate, pulse volume, tissues threads, Coronary arteries, long axes amplitudes, and left ventricular function

Drugs	Form and dose	Blood Pressure#	HR	Pulse volume*	Tissues Threads				Coronary arteries	Long axes	LV function
					Gastric		Paranasal Sinuses				
					Extensions	Echogenicity	Extensions	Echogenicity			
Aspirin	Tab 75 mg	NE	NE	NE	↓	↓	↓	↓	↑	↑	↑
Clopidogrel	Tab 75 mg	NE	NE	NE	↑	↑	↑	↑	↑	↑	↑
	Tab 150 mg	↓	↑	NE	↓	↓	↓	↓	↑↑	↑↑	↑↑
Atorvastatin	Tab 10 mg	↓	↑	Improved	↓	↓	↓	↓	↑	↑	↑
Rosuvastatin	Tab 10 mg	↓	NE	NE	↓	↓	↓	↓	↑	↑	↑

Simvastatin	Tab 10 mg	↓	↑	Improved	↓	↓	↓	↓	↑	↑	↑
Clarithromycin	Tab 250 mg	↑	↑	Improved	↓	↓	↓	↓	↑	↑	↑
Ginkgo biloba capsule	Cap 80 mg	↓	↓	NE	↓	↓	↓	↓	↑	↑	↑
Rumalaya forte tabs	Tab	↓	NE	NE	↓	↓	↓	↓	↓	↓	↓

***Pulse volume is improved by using of Clarithromycin, Simvastatin or Atorvastatin.# Blood pressure of hypertensive patients.**

5-Discussion.

In a prior study, the full-length examination of coronary arteries using color flow echocardiography revealed several diagnostic patterns of coronary artery disease, including stenosis, tortuosity, and the "strings of beads" sign (Figures 1, 2, 10) [3]. Although this pattern is typically associated with fibromuscular dysplasia in middle-aged females [4, 5], it has also been documented in elderly males with renal atherosclerosis [6]. In earlier work, the researcher found this pattern in both coronary and renal arteries across all age groups [3, 7].

In the current study, the "strings of beads" pattern reappeared in all 1,113 patients (500 females and 613 males) (Figures 1, 2, 3, 13, 14, 20, 24). The study also examined the effects of various drugs and herbal formulations on coronary arteries, long-axis amplitudes (Figures 7–12), and left ventricular dimensions and functions (Tables 2–3). A crucial observation was the delayed coronary flow characterized by an inverted systolic/diastolic ratio (Figure 21), indicating reduced myocardial perfusion.

After therapy, this ratio normalized, and diastolic flow significantly improved—reflecting restored myocardial perfusion [8]. The researcher believes this rapid normalization, accompanied by the reappearance and expansion of coronary arterial networks, highlights the immediate beneficial effects of clopidogrel (150 mg), low-dose statins, ginkgo biloba, and rumalaya forte. Similar vascular responses were previously documented in renal arteries after 30 minutes of drug intake [9]. These results, in the researcher's view, confirm that the drugs relieve transient vasoconstriction and stenosis, enhancing perfusion and cardiac contractility.

The further questions how such rapid physiological improvements occur before drug metabolism. He posits that these effects arise from the **stimulation of cytokine release** upon the initial contact of drug particles with the gastric mucosa. This hypothesis is supported by clinical evidence showing a sharp blood pressure drop (20/10–60/40 mmHg) and chest pain relief within 15 minutes—well before the hepatic activation of clopidogrel [10, 11]. Therefore, the researcher believes clopidogrel and low-dose statins may trigger vasodilatory and cardiotonic effects indirectly through **gastric-induced cytokine signaling.**

Cytokines—proteins that interact with specific cell receptors—regulate immune responses and cellular functions via autocrine, paracrine, and endocrine pathways [12, 13]. Accordingly, the researcher concludes that the **anti-inflammatory, immunomodulatory, antioxidant, and anti-fibrotic** effects of clopidogrel, statins, ginkgo biloba, rumalaya forte, and clarithromycin are mediated through the up- or down-regulation of cytokine pathways, as summarized in Table 5

Table (5): represents cytokines and effects on them by drugs and H. pylori

Cytokines	Clopidogrel	Atorva-statin	Rosuva-statin	Simva-statin	Ginkgo biloba	Rumalaya Forte	Aspirin	H.pylori
IL-1 alpha	Dec[14]		Inc [33]			DR[43]		Act[53, 54]
IL-1 beta	Dec [19,29]	Inc [30]	Dec[30]		Dec[39, 41]	DR[43]	Inc[49, 62]	Act[53, 54]
IL-2	Dec[14]		Inc [33]			DR[43] Enh[44		Act[54]

						(glycyrrhizin)		
IL-4			Inc[16]	Inc [35, 37]		UR[43]	NE[50]	
IL-5				Inc[35, 37]				
IL-6	Dec[14, 29]		Dec[16]		Inh[41]	DR[43, 48]	Inc[49] Dec[50]	Act[53, 54]
IL-8	Dec[15]		Inc[16]		Inh[40]	DR[44]		Act[53]
IL-10	Dec[14,29]	Inc [30, 31]	Dec[33]	Inc[38]	UR[39]	UR[43] Dec[48]	Inc[49] NE[50]	Act[53, 54]
IL-12						Enh[44]		Act[53, 54]
IL-13	Dec[14]			Inc[33, 37]				Act[54]
IL-17	Dec [19]	Dec [31]			DR[43]	Dec[45]		Act[53, 54]
IL-18		Dec[30]						Act[53, 54]
IL-21		Dec [30]						
IL-23		Dec [30]		Dec[37]				Act[53, 54]
IL-35		Dec [30]	Dec[30]					
IL-37		Inc [30]	Inc[30]					
IFN-gamma	Inc[29]	Dec [31]	NE [16]	Dec[35, 37]	Inh [63]	DR[43] Enh[44]	Red [62]	Act[53]
TNF-alpha	Dec[15]		Inc [16]		Dec[40, 41]	DR[43, 48]	Dec [50, 51]	Act[53]
TNF- beta	Dec[14]							
TGF-beta	Dec[16] Red[23]	Inc [30]	Dec[30]	Inc[35]	Inh [63]	ND	Inh[52,64] Inc [65]	Act[53]
P-selectin	Prev[16]							
ICAM-1	Red [17] [23]					Dec[46]		Act [96]
VCAM-1	Red [17]					Dec[46]		Act [96]
ERK	Supp.[17]							Act[56]
JNK	Supp[17]					UR[47]		Act[56]
ROS	Red[17]				Dec[41]		Dec [50]	
Nrf2	Act[17] UR [23, 84]	Act [66]	Act [67]	Act [68]	Ac[69]	ND	Act [70] Atten[71]	Inh [72]
NF-kB	Prev [18, 23]	Red [73]	Inh[74, 76]	Supp [75]	DR[42, 78]	Dec[48]	Mod[51] Inh[64]	Act.[56]
Ang II	Supp [18]				Inh[63]			
P2Y12	Inh[16]						NE [16]	
TLR2				Dec[60]				Act.[56,57]
TLR4	Act [78] Inh [16]	Supp [63]	Inh [79]	Dec[60]	Inh [77]	ND	NE[58] Inh[64]	Act.[54, 56]
Treg	Dec[28]	Reg [31]		Inc[35]	UR[43]			Induce[53]
VEGF	NE [20] Dec [22]		Inc[16]		Inh[40]	Dec[47]	Inc[52]	
VEGF-VEGFR2-ERK Signaling	Inh [11]							
PDGF-AB	NE [21] Dec[22]						Inc[52]	
MCP-1	Dec[23]	Dec[73]	Inc[16]					
SOCS3	ND			Inc[37]				
SOCS7	ND							
Foxp3	ND			Inc[35, 37]	Inc[43]	Dec[45]		Inc[53]
SMAD6	ND			Dec[35, 37]				
SMAD7	ND			Dec[35, 37]				

Diff. CD40	ND			Inc[35]				
Diff. Th17	ND			Dec[38]		PREV[45]		
GATA3	ND			Inc[36]				
JAK/STAT	ND			Dec[37]		PREV[45]		
STAT/NF-kB	Supp [23]							Act[56]
NLRP1	Inh[24]						Inh[24]	
NLRP3	Supp [23, 17]	Supp [59]	Inh [76]	Inh [79]	Inh [81]	ND	Inh [82]	Act [80]
TGF-b1/Smad3/ P2RY12 pathway	Blocked [17]							
TGF-b1/Smad2/ EMT pathway								Act[93]
Cox-1	NE[25]						Inh[52]	
Cox-2	NE[25]				DR[42]	Dec[47]	Inh[52]	
MMP9	ND					Dec [47]		
MAPK	Supp [26]				Mod[41]	Prev[48]		Act[56]
AMPK	Red [23] Act [84]				Mod[41]			
prostaglandin	NE[27]					Dec[43, 48]		
Eotaxin-1	ND					DR[43]		
iNOS	Inh[19]				Supp[61]		Dec[51]	
PPAR gamma	Reg [86]	Act [86]	Act [87]	Act [85]	Reg [83]	ND	Act [88]	DR[55]
ET-1	Inh*							
Fibronectin	Red [23]							
RANTES (ccl-5)	Supp [23]							
Th1/Th17		Dec [32]						
Th1		Dec [32]						
Th2		Inc [32]						
MMT		Inh [16]						
Leukotrienes						Dec[43]		
GM-CSF								Act[54]

Dec= decrease. Inc= increase. Reg = regulate. UR. = upregulate. DR. = down regulate. Prev. = prevention. Act. = activated. Supp = suppressive. Inh. = inhibition. MMT = Macrophage to Myofibroblast transition. Atten =Attenuates. Mod = modulate

H. Pylori and the TLR4-Mediated Inflammatory Response:

Many pro-atherogenic cytokines such as IL-1, TNF-α, and IFN-γ contribute to lipid metabolism disorders and chronic inflammation [89, 90]. This inflammatory state, largely mediated by TLR4 activation [92], plays a critical role in aging-related diseases [91]. TLR4, an innate immune receptor, responds to bacterial lipopolysaccharide (LPS) and endogenous ligands produced during inflammation [94, 95].

Gastric *H. pylori* infection exemplifies this mechanism. The bacteria induce structural changes in the gastric mucosa [96], forming long, branching "threads" (Figures 5, 6, 26) where bacteria persist. These structures may continuously stimulate TLR4, maintaining chronic inflammation even after antibiotic therapy. *H. pylori* thus manipulates immune regulation by altering cytokine expression and activating key pathways including TLR4, TGF-β, NF-κB, and MAPK [54, 56, 93]. The researcher interprets these findings as evidence of persistent immune stimulation that sustains systemic inflammation.

Systemic TLR4 Activation and Disease:

The pro-inflammatory influence of *H. pylori* extends beyond the stomach, activating both TLR2 and TLR4 in epithelial tissues [54, 56, 58]. TLR4 upregulation has been documented in distant organs, such as atherosclerotic plaques [97], the aging brain [99], and cardiac and aortic tissues [91]. Furthermore, TLR4 agonists can trigger endothelin-1 release, leading to vasoconstriction [98]. The improvement in brain function and histology after administering tea polyphenols—a known TLR4

inhibitor—via nasogastric tube [99] underscores TLR4's central role in systemic inflammation and neurovascular health. The researcher believes this provides a mechanistic link between gastrointestinal inflammation and multisystem disease progression.

H. pylori's Impact on Immune Homeostasis:

H. pylori disrupts immune homeostasis by activating pro-inflammatory mediators (IL-1β, IL-2, IL-6, TNF-α) and signaling cascades (TLR2/4, NF-κB, NLRP3 inflammasome) [54, 56, 57, 80], while suppressing antioxidant and regulatory pathways such as Nrf2 and PPAR-γ [72, 55]. This imbalance promotes chronic inflammation that extends to various organs, impairing both histological and physiological functions. However, the reversal of TLR4-driven pathology—such as restored memory and hippocampal integrity after inhibition [99]—suggests that these inflammatory disorders may be reversible under targeted modulation.

Reversal of Pathological Changes and the Post-Pandemic Paradox:

Certain drugs, herbs, and foods may counteract the inflammatory sequelae of *H. pylori* and SARS-CoV-2 through TLR pathway modulation. Clarithromycin, for instance, inhibits gastric TLR4 expression and downregulates pro-inflammatory cytokines (IL-12, IL-18) induced by *H. pylori* [101, 102]. Clinically, this translates into improved cardiac function, normalized blood pressure in both hypertensive and hypotensive patients, and enhanced peripheral circulation. Moreover, clarithromycin regulates intestinal motility and aids in shedding abnormal gastric and paranasal sinus tissue threads (Figure 26) by reducing inflammatory cytokines and growth factors, downregulating LPS-induced TLR4, and upregulating CTLA-4—an essential immune checkpoint protein [100–102]. The researcher views these effects as evidence of a systemic anti-inflammatory mechanism capable of reversing chronic pathological processes

Drug Effects and the Post-COVID-19 Era:

Low-dose clopidogrel previously showed minimal effect on inflammatory protein upregulation in diabetic mice [19]; however, our study demonstrates that a higher dose (150 mg) is necessary to reduce inflammation, induce vasodilation, lower blood pressure, enhance cardiac contractility, and inhibit fibrosis. The researcher believes these effects occur primarily at the gastric level, modulating key "controller points" within TLR pathways.

The TLR4 pathway, implicated in persistent inflammation and aging-related disorders [91], can be inhibited by clopidogrel [17]. This reduces pro-inflammatory cytokines such as IL-1α and IL-1β [14, 19, 29], thereby decreasing vasoconstrictive agents like endothelin-1. Clinically, this manifested as reduced effort-induced fatigue and improved coronary visibility within 30 minutes of drug intake (Figures 2C, E, F, 14–16, 21).

Conflicting evidence exists on clopidogrel's action on TLR4: some studies report inhibition [17], others activation [78], especially post-COVID-19. Unpublished data indicate that low-dose clopidogrel's benefits diminished post-pandemic, with paradoxical increases in blood pressure at 150 mg (mid-2025). Similarly, Simvastatin shifted from activating to reducing IFN-γ, and Aspirin's effect on TGF-β changed from activating to suppressive [34, 36, 64, 65]. These observations highlight that SARS-CoV-2 variants fundamentally alter inflammatory pathways and drug responses, necessitating a review of therapeutic strategies in the post-pandemic era.

A Shared Inflammatory Pathway:

H. pylori and SARS-CoV-2 trigger similar pro-inflammatory cascades, including TGF-β, NF-κB, TLR4, MAPK, and NLRP3 [54–56, 80, 103–105], while inhibiting regulatory pathways such as PPAR-γ and Nrf2 [55, 61, 106, 107]. The researcher interprets this shared profile as a common inflammatory mechanism that the discussed drugs effectively target. Their consistent

ability to reverse pathology indicates action on a fundamental inflammatory process, whether chronic (H. pylori) or acute-on-chronic (SARS-CoV-2).

Links to Atherosclerosis and Fibromuscular Dysplasia:

Inflammatory markers activated by H. pylori and SARS-CoV-2 are also characteristic of atherosclerosis (AS) and fibromuscular dysplasia (FMD) [93, 108, 109]. The similarity, including ICAM-1 and VCAM-1 activation [108–110], suggests H. pylori may contribute to or trigger FMD and AS. The researcher proposes advanced imaging or histological examination to identify the "EYE-SIGN" in affected tissues—a known indicator of H. pylori-induced inflammation.

Pathogenic Synergy and Therapeutic Implications:

Several researchers have proposed *H. pylori* as a pathogenic cofactor in multiple diseases, including COVID-19 [2]. The coexistence of SARS-CoV-2 and chronic *H. pylori* infection appears to intensify inflammation, forming dense, "ball-like" masses in gastric tissues. Since both pathogens are linked to cardiovascular disease, viral infection can exacerbate atherosclerosis (AS) and fibromuscular dysplasia (FMD). The researcher believes that therapeutic strategies modulating shared inflammatory pathways—such as those described previously [9]—may reverse this complex, multi-system pathology.

Evolving Treatment Strategies in the Post-Pandemic Era:

Drug efficacy and administration routes must be continuously adjusted due to persistent and sequential changes in SARS-CoV-2 variants. Between 2022 and early 2025, 150 mg clopidogrel with a statin sufficed. From April–July 2025, effective anticoagulants shifted to aspirin and Ginkgo biloba. By late July, two-drug regimens became insufficient, necessitating multi-drug therapies, with substitutions including clarithromycin, amoxicillin, cefixim, cefadroxil, and *Emblica officinalis* by late August 2025. The researcher interprets these shifts as evidence of the virus dynamically altering inflammatory responses, requiring adaptive treatment strategies.

The Cytokine-Mediated Mechanism:

These dynamic adjustments are necessary because emerging viral variants activate distinct cytokine profiles. Drugs with synergistic pro-inflammatory effects may worsen outcomes. For example:

- Variants activating IL-1α: rosuvastatin or simvastatin may exacerbate symptoms.
- Variants activating IL-1β: atorvastatin may worsen the patient's condition.
- Variants activating IFN-γ: clopidogrel or simvastatin alone may be detrimental.

The researcher emphasizes that drug choice and combinations must be tailored to counteract variant-specific inflammatory pathways, with additional agents used to inhibit harmful cytokines and ensure clinical improvement.

Therapeutic Regulation of the Immune Response:

Targeting TLR4 alone is inadequate due to complex cytokine interactions; even IL-10 can trigger JAK/STAT pathways, affecting pro-inflammatory genes [89]. Cytokines like IL-2 and IL-10 may unintentionally aid pathogens such as H. pylori and SARS-CoV-2 [111]. Therefore, complete TLR4 inhibition is suboptimal; targeted regulation of TLR signaling, achievable with drugs like clarithromycin, is required. The researcher emphasizes that therapeutic regimens must adapt continuously to circulating SARS-CoV-2 variants and new H. pylori exposures to ensure efficacy and prevent paradoxical effects.

Key Findings and Clinical Implications:

- **Diagnostic and Imaging Methods**

– Color flow and transthoracic echocardiography provide effective, non-invasive approaches for early diagnosis and follow-up of coronary artery disease and myocardial perfusion abnormalities.

- Doppler ultrasonography reliably identifies vascular signs of both atherosclerosis (AS) and fibromuscular dysplasia (FMD) in the same patients.
- Gastric and paranasal sinus ultrasound offers a simple method to monitor the effectiveness of drug therapies by observing tissue threads and wall changes.

- **Drug Efficacy and Pathology**

- High-dose clopidogrel (150 mg) with an appropriate statin significantly regulates blood pressure, enhances cardiac contractility, and reduces coronary stenosis by 20–30% within 15–30 minutes.
- Clarithromycin modulates cardiac, vascular, and blood pressure functions while facilitating the reduction and clearance of H. pylori–induced tissue threads.
- Improvements in fibrosis, seen as decreased hyperechogenicity on echocardiograms, can serve as rapid indicators of therapeutic success.

- **Pathogenesis and Therapeutic Direction**
  - H. pylori is a primary contributor to vascular diseases (AS, FMD), with SARS-CoV-2 amplifying inflammation.
  - Shared cytokine profiles indicate a common inflammatory mechanism, amenable to targeted therapy.
  - Effective drugs function as "controller point regulators," modulating CTLA-4 and TLR4 to reverse tissue pathology.
  - Coronary network decline and collateral vessel stenosis highlight the need to control underlying inflammation to prevent re-stenosis and organ injury

Recommendations.

1. Adopt non-invasive, cost-effective diagnostics (cardiac/abdominal ultrasound) for faster detection and improved patient outcomes.
2. Personalize therapeutic regimens based on circulating SARS-CoV-2 variants to avoid paradoxical drug effects.
3. Include comprehensive H. pylori screening and treatment in cardiovascular disease guidelines.
4. Develop drugs targeting key inflammatory pathways (e.g., TLR4, CTLA-4) rather than just alleviating symptoms.
5. Implement long-term pharmacovigilance for adverse or paradoxical drug effects, especially with emerging pathogens.
6. Educate clinicians on variable drug and herb effects depending on patients' inflammatory states.
7. **Further Research:**

- Histological and imaging studies to confirm H. pylori–induced markers in AS and FMD tissues.
- Comparative analyses of cytokines, growth factors, and receptors in AS, FMD, H. pylori, and SARS-CoV-2 to validate mechanistic links.
- Controlled studies to determine how SARS-CoV-2 variants alter therapeutic efficacy of drugs like clopidogrel and statins.

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References.

1. Thanassoulis G., Aziz H. (2022). Atherosclerosis, https://www.msdmanuals.com/home/heart-and-blood-vessel-disorders/atherosclerosis/atherosclerosis
2. He J, Liu Y, Ouyang Q, Li R, Li J, Chen W, Hu W, He L, Bao Q, Li P and Hu C (2022) Helicobacter Pylori and unignorable extragastric Diseases: Mechanism and implications. Front. Microbiol. 13:972777 Https://doi.org/10.3389/fmicb.2022.972777.

3. Al-Ashwal NSM. (2022). Examination of whole lengths of coronary arteries by color flow echocardiography, Journal of Medical & Pharmaceutical Sciences 6(6): 49 – 70. https://doi.org/10.26389/AJSRP.L070322.
4. Niepen, P.V., Robberechts, T., Devos, H., Tussenbroek, F., Januszewicz, A., Persu, A. (2021). Fibromuscular dysplasia: its various phenotypes in every day practice in 2021. Kardiol Pol. 79 (7-8): 733-744. https://doi.org/10.33963/KP.a2021.0040
5. Higashi, H. Inaba, S., Ogimoto, A., Okura, T., Higaki, J., Okayama, H. (2011). Atherosclerosis renal artery stenosis mimicking fibromuscular dysplasia, EJVES Extra 2011; 22, e44-e47. https://doi.org/10.1016/j.ejvs.2011.07.oo7
6. Mota, R., Homeister, J. w., Willis, M. S., Bahnson, M. (2017). Atherosclerosis: Pathogenesis, Genetics, and Experimentals Models, online, https://doi.org/10.1002/9780470015902.a0005998.pub3
7. Al-Ashwal, Nashwan Saleh Mohammed. (2024). Examination of renal vessels by Doppler ultrasound to see renal & peri-renal vascular features in patients with or without renal disease, Journal of Arbian Peninsula Centre for Medical and Applied Researches 1(2):23 – 41. https://doi.org/10.56793/pcra23122.
8. Motwani M., Fairbairn, T. A., Larghat A., Mather A. N., Biglands, J. D., Radjenovic A., Greenwood J. P., Plein S. (2012). Systolic versus Diastolic Acquisition in Myocardial Perfusion MR Imaging, Radiology: Volume 262: No. 3 March. https://doi.org/101148/radiol.11111549
9. Al-Ashwal N.S.M. (2024). Effect of drugs, medical herbal substances, fruits, coffee and tea on renal vessels in patients with and without renal failure, Journal of the Arabian Peninsula Center for Medical and Applied Research, 1(2), 100 – 125. https://doi.org/10.56793/pcra23126
10. Gurbel P. A., Bliden K. P., Butler K., Tantry U. S., et al, (2009). Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease, Circulation.120:2577-2585. Https://doi.org/10.1161/CIRCULATIONAHA.109.912550
11. Kuszynski D. S., and Lauver D. A. (2022). Pleiotropic effects of clopidogrel, Purinergic Signaling 18: 253 – 265. https://doi.org/10.1007/s11302-022-09876-0
12. Gray S. M., Bloch M. H. (2012). Systematic Review of Proinflammatory Cytokines in Obsessive-Compulsive Disorder, Curr Psychiatry Rep.14(3):220–228. Https://doi.org/10.1007/s11920-012-0272-0.
13. Lázár-Molnár E, Hegyesi H, Tóth S, Falus A. (2000). Autocrine and paracrine regulation by cytokines and growth factors in melanoma. Cytokine. 12(6):547-54. Https://doi.org/10.1006/cyto.1999.0614.
14. Antonino M. J., Mahla E., Bliden K. P., Tantry U. S., & Gurbel P. A. (2009). Effect of long term clopidogrel treatment on platelet function and inflammation in patients undergoing coronary artery disease: Biomarker profile and long-term clopidogrel. American Journal of Cardiology. https://doi.org/10.1016/j.amjcard.2009.01.367
15. Al-Bahrani, A., Taha, S., Shaath, H., and Bakhiet, M. (2007). TNF-alpha and IL-8 in acute stroke and the modulation of these cytokines by antiplatelet agents. Curr Neurovasc Res 4(1): 31 – 37. Https://doi.org/10.2174/156720207779940716.
16. Chen, J., Tang, Y., Zhong, Y., Wei, B., Huang, X. R., Ming, P., Tang, K., Xu, A., and Lan, H. (2022). P2Y12 inhibitor clopidogrel inhibits renal fibrosis by blocking macrophage to myofibroblast transition. Mol Ther. 5;30(9):3017–3033. Https://doi.org/10.1016/j.ymthe.2022.06.019.
17. Li, B., Zhang, Y., Zheng, Y., and Cai, H. (2024). The mechanisms and therapeutic potential of clopidogrel in mitigating diabetic cardiomyopathy in db/db mice. iScience, 27, 109134. https://doi.org/10.1016/j.isci.2024.109134
18. Pels, K., Schwimmbeck, P. L., Rosenthal, P., Loddenkemper, C., Dang-Heine, C., Rauch, U., Martens, H., Schultheiss, H. P., Dechend, R., Deiner, C. (2009). Long-term clopidogrel administration following severe coronary injury reduces proliferation and inflammation via inhibition of nuclear factor-kappaB and activator protein 1 activation in pigs. Eur J Clin Invest. 39(3):174-82. Https://doi.org/10.1111/j.1365-2362.2009.02089.x.
19. Heitzer, T., Rudolph, V., Schwedhelm, E., Karstens, M., Sydow, K., Ortak, M., Tschentscher, P., Meinertz, T., Boger, R., and Baldus, S. (2006). Clopidogrel improves systemic endothelial nitric oxide bioavailability in patients with coronary artery disease: Evidence for antioxidant and anti-inflammatory effects. Atherosclerosis, Arterioscler Thromb Vasc Biol 26(7):1648-52. Https://doi.org/10.1161/01.ATV.0000225288.74170.dc.
20. An X., Jiang G., Cheng C., Lv Z., Liu Y., Wang F. (2018). inhibition of platelets by clopidogrel suppressed Ang II-induced vascular inflammation, oxidative stress, and Remodeling, j Am Heart Assoc. 7:e009600. https://doi.org/10.1161/JAHA.118.009600
21. Smadja D. M., Bura A., Szymezak J., Blanchard A., Remones V., Azizi M., Gaussem P. (2012). Effect of clopidogrel on circulating biomarkers of angiogenesis and endothelial activation, Journal of Cardiology, 59(1):30 – 35. https://doi.org/10.1016/j.jjcc.2011.09.002
22. Gonzalez M., Arteaga-Vizcaino M., Ruiz A., Briceno O. (2013). PDGF and VEGF levels in platelet rich plasma, Journal of Dentists 1(1):16 – 23. https://doi.org/10.12974/2311-8695.2013.01.01.3

23. Gebeshuber C. A., Daniel-Fischer L., Regele H., Schachner H., Aufricht C., Kornauth C., Ley M., Alper S. L., Herzog R., Kratochwill K., Perco P. (2023). Computational drug repositioning of clopidogrel as a novel therapeutic option for focal segmental glomerulosclerosis, Translational Research, 259: 28 – 34. https://doi.org/10.1016/j.trsl.2023.04.001
24. Bleda S, De Haro J, Sanchez I, Laime I, Acin F. (2020). Effect of clopidogrel vs. aspirin on pro-atherosclerotic NLRP-1 inflammasome expression in endothelial cells. ECLOAS study. Clin Investig Arterioscler. 32(5):193-199. https://doi.org/10.1016/j.arteri.2020.03.002
25. Fitzgerald D. J., and FitzGerald G. A. (2013). Historical Lessons in translational Medicine: Cyclooxygenase inhibition and P2Y12 Antagonism, Circ Res. 112(1): 174 – 194. https://doi.org/10.1161/CIRCRESAHA.111.300271.
26. Ryu JH, Kim SJ. (2011). Clopidogrel effectively suppresses endothelial microparticle generation induced by indoxyl sulfate via inhibition of the p38 mitogen-activated protein kinase pathway. Blood Purif. 32(3):186-94. https://doi.org/10.1159/000326297.
27. Meune C., Mahe I., Solal A. C., Levy B. I., Duboc D., Simoneau G., Champion K., Mourad J-J., Weber S., Bergmann J-F. (2004). Comparative effect of aspirin and clopidogrel on arterial function in CHF, International Journal of Cardiology, 106(1):61 – 66. https://doi.org/10.1016/j.ijcard.2004.12.059..
28. Vemulapalli H, Samara A, Tsygankov AY, Liverani E. (2018). Blockade of the P2Y12 signaling pathway with Clopidogrel restrains Treg proliferation in vivo during sepsis and in vitro, Blood 132(1):2413. https://doi.org/10.1182/blood-2018-99-114884.
29. Garcia A. E., Mada S. R., Rico M. C., De La Cadena R. A., Kunapuli S. P. (2011). Clopidogrel, a P2Y12 receptor antagonist potentiates the inflammatory response in a rat model of peptidoglycan polysaccharide induced arthritis, Blood, 118(21):3287. https://doi.org/10.1182/blood.V118.21.3287.3287.
30. Wozniak E., Broncel M., Niedzielski M., Wozniak A., and Pabis P. G. (2023). The effect of lipid lowering therapies on the pro-inflammatory and anti-inflammatory properties of vascular endothelial cells. PLOS ONE, 18(2), e0280741. https://doi.org/10.1371/journal.pone.0280741.
31. Eller P., Eller K., Wolf A. M., and Oberhuber G. (2010). Atorvastatin attenuates murine anti-glomerular basement membrane glomerulonephritis. Kidney Int 77(5):428-35. Https://doi.org/10.1038/ki.2009.478.
32. Li X. L., Liu Y., Cao L. L., Zhang P., Yan W. X., Shen H. H., and Zuo Z. X. (2013). Atorvastatin modified dendritic cells in vitro ameliorate experimental autoimmune myasthenia gravis by up-regulated Treg cells and shifted Th1/Th17 to Th2 cytokines. Molecular and Cellular Neuroscience, 56(1), 85-95. https://doi.org/10.1016/j.mcn.2013.03.003.
33. Vavlukis A, Vavlukis M, Dimovski A, Petrushevska G, Eftimov A, Domazetovska S, Mladenovska K. (2021). Anti-inflammatory and immunomodulatory effects of rosuvastatin in patients with low-to-moderate cardiovascular risk. Acta Pharm. 72(2):303-315. Https://doi.org/10.2478/acph-2022-0018. PMID: 36651514.
34. Zhang X., Jin J., Peng X., Ramgolam V. S., and Markovic-Plese, S. (2008). Simvastatin inhibits IL-17 secretion by targeting multiple IL-17 regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in CD4+ lymphocytes..J Immunol 15;180(10):6988-96. Https://doi.org/10.4049/jimmunol.180.10.6988.
35. Kim Y. C., Kim K. K., and Shevach E. M. (2010). Simvastatin induces Foxp3+ T regulatory cells by modulation of transforming growth factor-beta signal transduction. Immunology, 130(4), 484-493. https://doi.org/10.1111/j.1365-2567.2010.03398.x.
36. Arora M., Chen L., Paglia M., Gallagher A., Allen M., and Manickam M. (2006). Simvastatin promotes Th2-type responses through the induction of the chitinase family member Ym1 in dendritic cells. Proc Natl Acad Sci U S A 103(20), 7777-82. Https://doi.org/10.1073/pnas.0508492103.
37. Lee K. J., Moon J. Y., Choi H. K., Kim K. K., and Lee S. H. (2010). Immune regulatory effects of Simvastatin on regulatory T cell-mediated Tumor Immune tolerance. Clinical and Experimental Immunology, 161(2), 298-305. Https://doi.org/10.1111/j.1365-2249.2010.04170.x.
38. Chamani S., Kooshkaki O., Moossavi M., Rastegar M., Soflaei S. S., McCloskey A. P., Banach M. and Sahebkar A. (2023). The effects of statins on the function and differentiation of blood cells. Archives of Medical Science, 19(5), 1314-1326. https://doi.org/10.5114/aoms/158546.
39. Jiao YB, Rui YC, Yang PY, Li TJ, Qiu Y. (2007). Effects of Ginkgo biloba extract on expressions of IL-1beta, TNF-alpha, and IL-10 in U937 foam cells. Yao Xue Xue Bao. 42(9):930-4. PMID:18050733.
40. Trompezinski S., Bonneville M., Pernet I., Denis A., Schmitt D., and Viac J. (2010). Ginkgo biloba extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. Archives of Dermatological Research, 302, 183- 189. https://doi.org/10.1007/s00403-009-0979-x
41. Li Y., Zhu X., Wang K., Zhu L., Murry M. and Zhou F. (2022). The potential of Ginkgo biloba in the treatment of human diseases and relationship to Nrf2-mediated antioxidant protection. Journal of Pharmacy and Pharmacology, 74, 1689 – 1699. https://doi.org/10.1093/jpp/rgac036

42. Zou X, Liu S, Zou H, Zhou W, Fu H, Wei J, Zhang J, Zeng H, Tan T, Zhou W, Wu H, Chen X, Zhou X. (2023). Inflammatory mechanisms of Ginkgo Biloba extract in improving memory functions through lncRNA-COX2/NF-ΚB pathway in mice with status epilepticus. CNS Neurosci Ther. 29(1):471-482. Https://doi.org/10.1111/cns.14019
43. Ammon H. P. T. (2011). Erratum to Modulation of the immune system by Boswellia Serrata extracts and Boswellic acids. Phytomedicine, 18(4), 334. https://doi.org/10.1016/j.phymed.2011.01.009
44. Matsui S., Matsumoto H., Sonoda Y., Ando K., Yokota E. A., Sato T. and Kasahara T. (2004). Glycyrrhizin and related compounds down-regulate production of inflammatory chemokines IL-8 and exotoxin-1 in a human lung fibroblast cell line. International Immunopharmacology, 4, 1633 – 1644. https://doi.org/10.1016/j.intimp.2004.07.023
45. Nandan A., Sharma V., Banerjee P., Sadasivam K., Venkatesan S. and Prasher B. (2022). Deciphering the mechanism of Tinospora Cordifolia extract on Th17 cells through in depth transcription profiling and in silico analysis. Frontiers in Pharmacology, 13, 1056677. https://doi.org/10.3389/fphar.2022.1056677
46. Fard, E. A., Fereydouni Z., Mansouri K. and Mostafa A. (2020). Effect of Tribulus terrestris L. on expression of ICAM-1, VCAM-1, E-Selectin and proteome profile of human endothelial cells in vitro. Iranian Journal of Immunology, 17(1):64 – 67. https://doi.org/10.22034/iji.2020.80295
47. Kunnumakkara A. B., Banik K., Bordoloi D., Harsha C., Choudhary, Sailo B. L., Padmavathi G., Roy N. K., Gupta S. C. and Aggarwal B. B. (2018). Googling the Guggul (Commiphora and Boswellia) for prevention of chronic diseases. Frontiers in Pharmacology, 9;686. https://doi.org/10.3389/fphar.2018.00686
48. Hwalee H., Ahn E. K., Hong S. S. and Oh J. S. (2017). Anti-inflammatory effects of Tribulusamide D isolated from Tribulus terrestris in lipopolysaccharide stimulated RAW264.7 macrophages. Molecular Medicine Reports, 16, 4421 – 4428. https://doi.org/10.3892/mmr.2017.7208
49. Brox R, Hackstein H. (2021). Physiologically relevant aspirin concentration trigger immunostimulatory cytokine production by human leukocytes. PLoS ONE 16(8): e0254606. https://doi.org/10.1371/journal.pone.0254606
50. Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, Davey CG, Sanna L, Maes M. (2013). Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Med.18;11:74. Https://doi.org/10.1186/1741-7015-11-74. PMID: 23506529; PMCID: PMC3751197.
51. El Kasmi KC, Stenmark KR. (2015). Contribution of metabolic reprogramming to macrophage plasticity and function. Semin Immunol. 27(4):267-75. Https://doi.org/10.1016/j.smim.2015.09.001. Epub 2015 Oct 9. PMID: 26454572; PMCID: PMC4677817.
52. Frey C., Yeh P. C., and Jayaram P. (2020). Effects of antiplatelet and nonsteroidal anti-inflammatory medications on platelet-rich plasma, A systematic review, The Orthopedic Journal of Sports Medicine, 8(4), 2325967120912841. https://doi.org/10.1177/2325967120912841
53. Mitchel P. J., Afzali H., Fazekasova H., Chen D., Ali N., Powell N., Lord G. M., Lechler R. I., and Lombardi G. (2021). Helicobacter pylori induces in-vivo expansion of human regulatory T cells through stimulating interleukin-1beta production by dendritic cells, Clinical & Experimental Immunology, 170:300-309. Https://doi.org/10.1111/j.1365.2012.04659.x
54. Figueiredo A. C., Marques C. R., Costa R. dos S., F da Silva H. B., Alcantra-Neves N. M. (2014). Cytokines gene polymorphisms and Helicobacter pylori infection: Friend or foe?, World J Gastroenterol 14; 20(18): 5235-5243. https://doi.org/10.3748/wjg.v20.i18.5235.
55. Yang S., Xia Y. P., Luo X. Y., Chen S. L., Li B. W., Ye Z. M. et al. (2019). Exosomal CagA derived from Helicobacter pylori infected gastric epithelial cells induces macrophage foam cell formation and promotes atherosclerosis. J. Mol. Cell Cardiol 135, 40 – 51. https://doi.org/10.1016/j.yjmcc.2019.07.011.
56. Re, F., Strominger J. L. (2004). Heterogeneity of TLR-induced responses in dendritic cells (DCs): from innate to adaptive immunity, Immunobiology, 209(1-2): 191 – 198. Https://doi.org/10.1016/j.imbio.2004.03.005.
57. Ding S. Z., Torok A. M., Smith M. F., Goldberg J. B. (2005). Toll-like receptor 2-mediate gene expression in epithelial cells during Helicobacter pylori infection, Helicobacter, 10(3):193 – 204. Https://doi.org/10.1111/j.1523-5378.2005.00311.x.
58. Hally K. E., La Flamme A. C., Harding S. A. and Larsen P. D. (2018). The effects of aspirin and ticagrelol on Toll-like receptor (TLR) mediated platelet activation: results of a randomized cross-over trial. Platelets, 30(5): 599 – 607. https://doi.org/10.1080/09537104.2018.1479520
59. Kong F, Ye B, Lin L, Cai X, Huang W, Huang Z. (2016). Atorvastatin suppresses NLRP3 inflammasome activation via TLR4/MyD88/NF-ΚB signaling in PMA-stimulated THP-1 monocytes. Biomed Pharmacother. 82:167-72. Https://doi.org/10.1016/j.biopha.2016.04.043.
60. Moutzouri E, Tellis CC, Rousouli K, Liberopoulos EN, Milionis HJ, Elisaf MS, Tselepis AD. (2012). Effect of simvastatin or its combination with ezetimibe on Toll-like receptor expression and lipopolysaccharide - induced cytokine production in monocytes of hypercholesterolemic patients. Atherosclerosis. 225(2):381-7. Https://doi.org/10.1016/j.atherosclerosis.2012.08.037.

61. Kobuchi H., Droy-lefaix M. T., Christen Y, Packer L. (1997). Ginkgo biloba extract (egb 761): inhibitory effect on nitric oxide production in the macrophage cell line raw 264.7. Biochemical Pharmacology, 53(6):897-903 Https://doi.org/10.1016/S0006-2952(96)00873-8.
62. Kwon MS, Shim EJ, Seo YJ, Choi SS, Lee JY, Lee HK, Suh HW. (2005). Effect of aspirin and acetaminophen on proinflammatory cytokine-induced pain behavior in mice. Pharmacology. 74(3):152-6. Https://doi.org/10.1159/000084548. Epub 2005 Mar 17. PMID: 15775706.
63. YU X, SU Q, GENG J, LIU H, LIU Y, LIU J, SHI Y, and ZOU Y. (2021). Ginkgo biloba leaf extract prevents diabetic nephropathy through the suppression of tissue transglutaminase, Experimental and Therapeutic Medicine, 21: 333. Https://doi.org/10.3892/etm.2021.9764
64. SUN Y., LIU B., XIE J., JIANG X., XIAO B., HU X., and XIANG J. (2022). Aspirin attenuates liver fibrosis by suppressing TGF-β1/Smad signaling, Molecular Medicine REPORTS 25:181. Https://doi.org/10.3892/mmr.2022.12697
65. WANG Y., DU C., ZHANG N, LI M., LIU Y, ZHAO M., WANG F., and FENG LUO F. (2018).TGF-β1 mediates the effects of aspirin on colonic tumor cell proliferation and apoptosis, ONCOLOGY LETTERS 15: 5903-5909. Https://doi.org/10.3892/ol.2018.8047
66. Fan J, Zhang X, Chen R. (2022). Atorvastatin alleviates oxidative damage by activating the nuclear factor erythroid 2-related factor 2 pathway after brain ischemia in mice. Ann Transl Med. 10(20):1135. Https://doi.org/10.21037/atm-22-4565.
67. Wang P., Luo L., Shen Q., Shi G., Mohammed A., Ni S., Wu X. (2018). Rosuvastatin improves myocardial hypertrophy after hemodynamic pressure overload via regulating the crosstalk of Nrf2/ARE and TGF-b1/Smads pathways in rat heart, European Journal of Pharmacology,820:173-182, Https://doi.org/10.1016/j.ejphar.2017.12.013.
68. Jang HJ. HongEM. Park SW. Byun HW. Koh DH. Choi MH. Kae SH. Lee J. (2016). Simvastatin induces heme oxygenase-1 via NF-E2-related factor 2 (Nrf2) activation through ERK and PI3K/Akt pathway in colon cancer. Oncotarget. 7: 46219-46229. https://doi.org/10.3892/ol.2016.4569
69. Yue Li, Xue Zhu, Ke Wang, Ling Zhu, Michael Murray, Fanfan Zhou. 2022). The potential of Ginkgo biloba in the treatment of human diseases and the relationship to Nrf2—mediated antioxidant protection, Journal of Pharmacy and Pharmacology, 74(12)1689—1699, Https://doi.org/10.1093/jpp/rgac036
70. Wei W, Shurui C, Zipeng Z, Hongliang D, Hongyu W, Yuanlong L, Kang Z, Zhaoliang S, Yue G, Chang L, Mei X. (2018). Aspirin suppresses neuronal apoptosis, reduces tissue inflammation, and restrains astrocyte activation by activating the Nrf2/HO-1 signaling pathway. Neuroreport. 29(7):524-531. Https://doi.org/10.1097/WNR.0000000000000969. PMID: 29381509.
71. Gou Q, Xie Y, Gou Q, Liu Z, Ma J. (2023). Aspirin promotes ferroptosis by attenuating Nrf2 in triple-negative breast cancer, EUROPE PMC, Https://doi.org/10.21203/rs.3.rs-2586619/v1
72. Bacon S., Seeneevassen L., Fratacci A., Rose F., Tiffon C., Sifré E., Haykal M. M., Moubarak M. M., Ducournau A., Bruhl L., et al. (2022). Nrf2 Down regulation contributes to epithelial to mesenchymal transition in helicobacter pylori infected cells. Cancers 14,4316. Https://doi.org/10.3390/cancers14174316
73. Ortego M., Bustos C., Hernández-Presa M. A., Tuñón J., Díaz C., Hernández G., Egido J. (1999). Atorvastatin reduces NF-kB activation and chemokine expression in vascular smooth muscle cells and mononuclear cells, Atherosclerosis 147(2):253-261, Https://doi.org/10.1016/S0021-9150(99)00193-8.
74. Tang Z, Ning Z, Li Z. (2024). The beneficial effects of Rosuvastatin in inhibiting inflammation in sepsis. Aging (Albany NY).16(12):10424-10434. Https://doi.org/10.18632/aging.205937
75. Gu C., Wu Y., Fan Z., Han W. (2017). Simvastatin improves intracerebral hemorrhage through NF-ΚB-mediated apoptosis via the MyD88/TRIF signaling pathway, Exp Ther Med.15(1):377—382. Https://doi.org/10.3892/etm.2017.5349
76. Saleh DO, Abo El Nasr NM, Elbaset MA, Shabana ME, Esatbeyoglu T, Afifi SM, et al. (2025). Role of rosuvastatin and pitavastatin in alleviating diabetic cardiomyopathy in rats: Targeting of RISK, NF-ΚB/ NLRP3 inflammasome and TLR4/ NF-ΚB signaling cascades. PLoS One 20(7): e0325767. Https://doi.org/10.1371/journal.pone.0325767
77. Wen Y., Lin W., Wang W. (2025). Mechanism of total Ginkgo biloba flavone mediating the inflammation and autophagy in lipopolysaccharide-induced human coronary artery endothelial cells through TLR4/PI3K signaling pathway, Journal of Radiation Research and Applied Sciences,18(3)101712. Https://doi.org/10.1016/j.jrras.2025.101712.
78. Jiang Z, Wang Z, Wang Z, Li C, Zhang Z, Sun W. (2019). The activation of high mobility group Box1 and toll-like receptor 4 is involved in clopidogrel-induced gastric injury through p38 MAPK. Pharmazie. 74(9):547-552. Https://doi.org/10.1691/ph.2019.9446. PMID: 31484595.
79. Wang X, Huo R, Liang Z, Xu C, Chen T, Lin J, Li L, Lin W, Pan B, Fu X, Chen S. (2022). Simvastatin Inhibits NLRP3 Inflammasome Activation and Ameliorates Lung Injury in Hyperoxia-Induced Bronchopulmonary Dysplasia via the KLF2-Mediated Mechanism. Oxid Med Cell Longev. 2022:8336070. Https://doi.org/10.1155/2022/8336070

80. Pachathundikandi S. K, Blaster N, Bruns H, and Backert S. (2020). Helicobacter pylori Avoids the Critical Activation of NLRP3 Inflammasome-Mediated Production of Oncogenic Mature IL-1β in Human Immune Cells, Cancers 12, 803; Https://doi.org/10.3390/cancers12040803.
81. Zhang Y., Zhao Y., Zhang J., Gao Y., Li S., Chang C., Yu D., Yang G. (2021). Ginkgolide B inhibits NLRP3 inflammasome activation and promotes microglial M2 polarization in Aβ1-42-induced microglia cells, Neuroscience Letters,764;136206. Https://doi.org/10.1016/j.neulet.2021.136206.
82. Zhou X., Wu Y., Ye L.., Zhang K., Wang L., Huang Y., Wang L., Xian S., Zhang Y., Chen Y. (2019). Aspirin alleviates endothelial gap junction dysfunction through inhibition of NLRP3 inflammasome activation in LPS-induced vascular injury. Acta Pharmaceutica Sinica B 9(4):711-723 Https://doi.org/10.1016/j.apsb.2019.02.008
83. Cho YL., Park JG., Kang HJ., Kim W., Cho M. J., Jang JH., Kwon MG., Kim S., Lee SH., Lee J., Kim YG., Park YJ., Kim W. K., Bae KH., Kwon BM., Chung S. J., Min JK. (2019). Ginkgetin, a biflavone from Ginkgo biloba leaves, prevents adipogenesis through STAT5-mediated PPARγ and C/EBPα regulation, Pharmacological Research 139:325-336, Https://doi.org/10.1016/j.phrs.2018.11.027.
84. Tai T, Shao Y-Y, Zheng Y-Q, Jiang L-P, Han H-R,Yin N, Li H-D, Ji J-Z, Mi Q-Y, Yang L, Feng L, Duan F-Y and Xie H-G. (2024). Clopidogrel ameliorate high-fat diet-induced hepatic steatosis in mice through activation of the AMPK signaling pathway and beyond. Front. Pharmacol. 15:1496639 Https://doi.org/10.3389/fphar.2024.1496639
85. Zou C, Qi H, Liu ZH, Han L, Zhao C, Yang X. (2013). Simvastatin activates the PPARγ-dependent pathway to prevent left ventricular hypertrophy associated with inhibition of RhoA signaling. Tex Heart Inst J. 40(2):140-7. PMID: 23678211; PMCID: PMC3649785
86. Grip O, Janciauskiene S, Lindgren S. Atorvastatin activates PPAR-gamma and attenuates the inflammatory response in human monocytes. Inflamm Res. 2002 Feb;51(2):58-62. Https://doi.org/10.1007/BF02684000
87. Desjardins F, Sekkali B, Verreth W, Pelat M, De Keyzer D, Mertens A, Smith G, Herregods MC, Holvoet P, Balligand JL. (2008). Rosuvastatin increases vascular endothelial PPARgamma expression and corrects blood pressure variability in obese dyslipidaemic mice. Eur Heart J. 29(1):128-37. Https://doi.org/10.1093/eurheartj/ehm540.
88. Guo Y, Zhu Y, Sun Y, Yang H. (2022). The preventive effect of low-dose aspirin in a PPAR-γ antagonist treated mouse model of preeclampsia. BMC Pregnancy Childbirth. 22(1):606. Https://doi.org/10.1186/s12884-022-04901-x.
89. Kleemann R., Zadelaar S. and Kooistra T. (2008). Cytokines and atherosclerosis: a comprehensive review of studies in mice, Cardiovascular Research 79, 360 – 376. https://doi.org/10.1093/cvr/cvn120
90. Steinberg D. (2005). Hypercholesterolemia and inflammation in atherogenesis: two sides of the same coin. Mol Nutr Food Res 49: 995 – 998. Https://doi.org/10.1002/mnfr.200500081.
91. Kim H-J, Kim H., Lee J-H., Hwangbo C. (2023). Toll-like receptor 4 (TLR4): new insight immune and aging, 20:67. https://doi.org/10.1186/s12979-023-00383-3
92. Molteni M, Gemma S, Rossetti C. (2016). The Role of Toll-like receptor 4 in infectious and noninfectious inflammation. Mediators Inflamm. 2016:6978936. https://doi.org/10.1155/2016/6978936.
93. Tedgui A., Mallat Z. (2005). Cytokines in Atherosclerosis: Pathogenic and Regulatory Pathways. Physiological Reviews, 86(2):515-581. https://doi.org/10.1152/physrev.00024.2005.ffhal-01589451
94. Al-Ashwal Nashwan Saleh. (2020). Diagnosis of Helicobacter pylori: A guide to diagnosis of Helicobacter pylori by clinical and ultrasonography approaches, AGH. https://aghpublishing.com/product/book-02-3112020.
95. Smolinska M. J., Page T. H., Urbaniak A. M., Mutch B. E., and Horwood N. J. (2011). Hck Tyrosine Kinase regulates TLR4-induced TNF and IL-6 production via AP-1, The Journal of Immunology, 187:6043-6051. Https://doi.org/10.4049/jimmunol.1100967.
96. Fang Z., Zhang W., Wang H., Zhang C., Li J., Chen W., Xu X., Wang L., Ma M., Zhang S., Li Y. Helicobacter pylori promotes gastric cancer progression by activating the TGF-beta/Smad2/EMT pathway through HKDC1. Cell Mol life Sci. 15;81(1):453. https://doi.org/10.1007/s00018-024-05491-x
97. Edfeldt K, Swedenborg J, Hansson GK, Yan ZQ. (2002). Expression of toll-like receptors in human atherosclerotic lesions: a possible pathway for plaque activation. Circulation.105(10):1158-61. PMID: 11889007.
98. Spirig R, Potapova I, Shaw-Boden J, Tsui J, Rieben R, Shaw SG. (2009). TLR2 and TLR4 agonists induce production of the vasoactive peptide endothelin-1 by human dendritic cells. Mol Immunol. 46(15):3178-82. Https://doi.org/10.1016/j.molimm.2009.05.179.
99. Song C., Zhang Y., Cheng L., Shi M., Li X., Zhang L., Zhao H. (2021). Tea polyphenols ameliorates memory decline in aging model rates by inhibiting brain TLR/NF-kB inflammatory signaling pathway caused by intestinal flora dysbiosis. Exp Gerontol. 1;153:111476. https://doi.org/10.1016/j.exger.2021.111476.

100. Takemori N., Ooi HK., Imai G., Hoshino K. and Saio M. (2020). Possible mechanisms of action of clarithromycin and its clinical application as a repurposing drug for treating multiple myeloma,14:1088; https://doi.org/10.3332/ecancer.2020.1088
101. Sugiyama K., Shirai R., Mukae H., Ishimoto H., Nagata T., Sakamoto N., Ishii H., Nakayama S., Yanagihara K., Mizuta Y. and Kohno S. (2007). Differing effects of clarithromycin and azithromycin on cytokine production by murine dendritic cells. Clinical and Experimental Immunology, 147: 540-546. Https://doi.org/10.1111/j.1365-2249.2007.03299.x.
102. Hossen MM, Ma Y, Yin Z, Xia Y, Du J, Huang JY, Huang JJ, Zou L, Ye Z and Huang Z (2023) Current understanding of CTLA-4: from mechanism to autoimmune diseases. Front. Immunol. 14:1198365. Https://doi.org/10.3389/fimmu.2023.1198365.
103. Chatterjee B and Thakur SS (2022). SARS-CoV-2 Infection Triggers Phosphorylation: Potential Target For Anti-COVID-19 Therapeutics. Front. Immunol. 13:829474. Https://doi.org/10.3389/fimmu.2022.829474
104. Asaba CN, Ekabe CJ, Ayuk HS, Gwanyama BN, Bitazar R, Bukong TN. Interplay of TLR4 and SARS-CoV-2: Unveiling the Complex Mechanisms of Inflammation and Severity in COVID-19 Infections. J Inflamm Res. 2024 Jul 26;17:5077-5091. Https://doi.org/10.2147/JIR.S474707.
105. Albornoz EA, Amarilla AA, Modhiran N, Parker S, Li XX, Wijesundara DK, Aguado J, Zamora AP et al. SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein. Mol Psychiatry. 2023 Jul;28(7):2878-2893. Https://doi.org/0.1038/s41380-022-01831-0.
106. Qua Y., Haas de Mello A., Morris D. R., Jones-Hall Y. L., Ivanciuc T., Sattler R. A., Paessler S., Menachery V. D., Garofalo R. P., Casola A. (2023). SARS-CoV-2 Inhibits NRF2-Mediated Antioxidant Responses in airway epithelial cells and in the Lung of a Murine Model of Infection, Microbiology Spectrum 11(3). Https://doi.org/10.1128/spectrum.00378-23
107. Hasankhani A, Bahrami A, Tavakoli-Far B, Iranshahi S, Ghaemi F, Akbarizadeh MR, Amin AH, Abedi Kiasari B and Mohammadzadeh Shabestari A (2023) The role of peroxisome proliferator-activated receptors in the modulation of hyper inflammation induced by SARS-CoV-2 infection: A perspective for COVID-19 therapy. Front. Immunol. 14:1127358. Https://doi.org/10.3389/fimmu.2023.1127358
108. Ait-Oufella H., Taleb S., Mallat Z., Tedgui A. (2011). Recent Advances on the Role of Cytokines in Atherosclerosis, (Arterioscler Thromb Vasc Biol. 31:969-979.). Https://doi.org/10.1161/ATVBAHA.110.207415
109. Ganesh S. K., Morissette R., Xu Z., Schoenhoff F., Griswold B. F., Yang J., Tong L., Yang M-L., Hunker K., Sloper L., Kuo S., Raza R., Milewicz D. M., Francomano C. A., Dietz H. C., Eyk J. V., and McDonnell N. B. (2014). Clinical and biochemical profiles suggest Fibromuscular dysplasia is a systemic disease with altered TGF-Beta expression and connective tissue features, FASEB J. 28, 3313—3324. Https://doi.org/10.1096/fj.14-251207.
110. Innocenti M, Thoreson AC, Ferrero RL, Strömberg E, Bölin I, Eriksson L, Svennerholm AM, Quiding-Järbrink M. Helicobacter pylori-induced activation of human endothelial cells. Infect Immun. 2002 Aug;70(8):4581-90. Https://doi.org/10.1128/IAI.70.8.4581-4590.2002.
111. Al-Ashwal N.S. (2021). Medicinal herbs and manufactured drugs: for Treatment of COVID-19 and its complications. Journal of medical & pharmaceutical Sciences 5(1):1-28. Https://doi.org/10.26389/AJSRP.S091220