Pan-African Journal of Health And Psychological Sciences
ISSN: 3093-4737 | www.pajhps.org
Vol.2, No 1 | Jan-March 2026

# Uncovering Aristolochic Acid–Driven Mutational Signatures and Novel Biomarkers in Primary Hepatic Angiosarcoma for Targeted Therapeutic Development

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**Abstract**

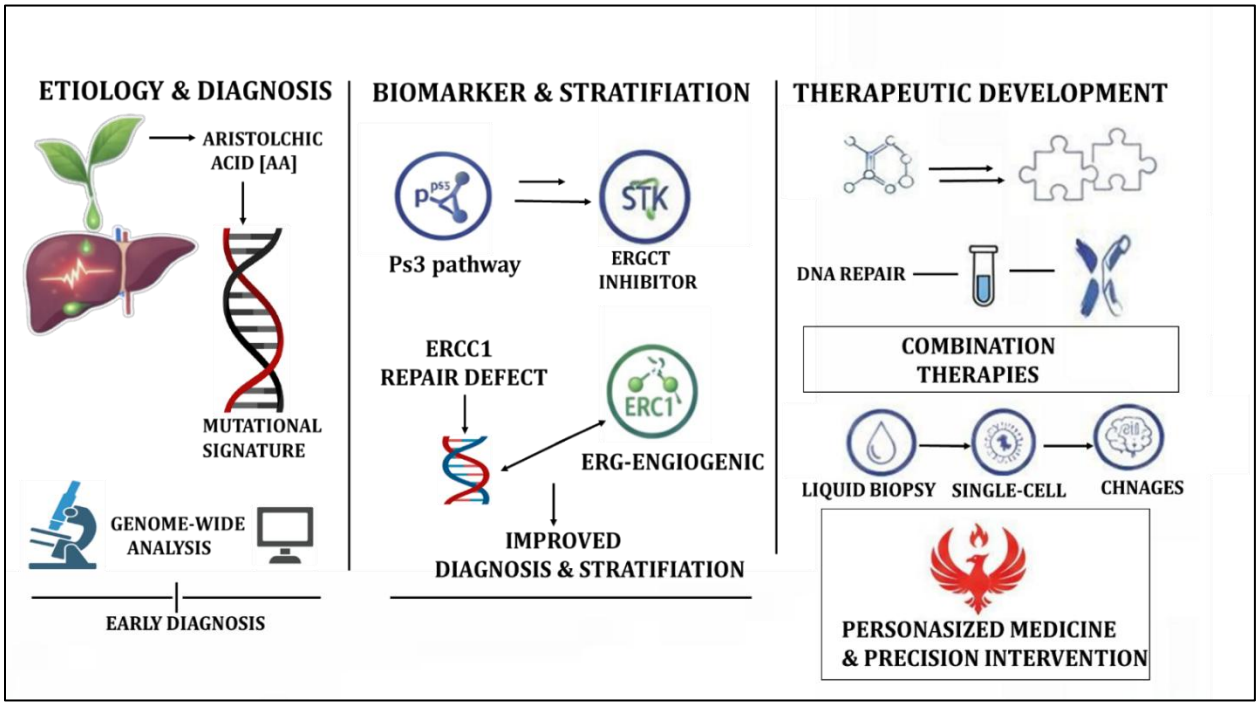
Primary hepatic angiosarcoma is a very rare and extremely aggressive malignancy that has had few therapeutic options and has been closely linked to aristolochic acid which is a strong environmental carcinogen commonly found in some herbal medicines. The hallmark mutational signature of aristolochic acid is the observed A: T↔ T: A transversion at context-specific trinucleotide motifs, and this pattern can be used to discriminatively identify AA-induced tumors with genome-wide analyses. This signature can act as a molecular signature that has the potential to explain the etiology of cancers, can aid retrospective exposure assessment, as well as contribute to early diagnosis. Coincidently, the molecular profiling has highlighted new biomarkers, serine/threonine kinase p53 pathways, aberrations of ERCC1 DNA repair enzyme, and up-regulation of endothelial cell markers. which have collectively enhanced diagnosis and stratification outcomes. These markers have been tested as potential predictive targets and provide the basis of precision approaches that encompass PARP inhibitors that target DNA-repair defects, targeted kinase inhibitors, and monoclonal antibodies against angiogenic pathways. Combination therapies that include the targeted with conventional chemotherapy have been shown to be more effective. Even more, the development of innovative technologies, including liquid biopsy, single-cell sequencing, and artificial intelligence-mediated searches in mutational signatures, further expand personalized medicine of Primary hepatic angiosarcoma and allow an earlier manifestation and precision intervention.

Mohammad, R. et al. (2026). **Uncovering Aristolochic Acid–Driven Mutational Signatures and Novel Biomarkers in Primary Hepatic Angiosarcoma for Targeted Therapeutic Development. Pan-African Journal of Health and Psychological Sciences. Vol. 2. No. 1. Jan-March 2026. https://doi.org/10.64261/55166d57.**

ISSN: 3093-4737

**Keywords: -** Aristolochic acid, mutational signature, hepatic angiosarcoma, DNA repair, targeted therapy, carcinogens.

**Graphical Abstract:** A brief overview of how biomarkers could be used in a diagnostic procedure, therapeutic evolution and facilitate individualized precision oncology is outlined.




## 1. Introduction

Primary hepatic angiosarcoma (PHA) is an unusually unusual and aggressive malignancy of the hepatobiliary system that stems out of an endothelial cell that is located within the vascular structure of the liver. Comprising less than 2 % of all primary hepatic neoplasms, the least effective time in PHA development is age of more than 60 years, with the highest incidence being at the 6th-7th decades (1). Abdominal pain, hepatomegaly, weight loss and, more rarely, jaundice and ascites are characteristic of symptomatic presentation being non-specific, such constitutional manifestations are often associated with the aggressive unrestricted vascular invasion and the rate of growth of

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tumour common in the disease. Thus, patients frequently appear with severe, bilateral disease and complication phenomena, including thrombocytopenia and spontaneous rupture of tumours, which leads to acute hemoperitoneum (2). Radiological study presents them with heterogeneous, irregular masses containing implied haemorrhagic elements and exuberant contrast enhancement. The overall prognosis is dismal with a median survival of less than 6-12 months following the diagnosis mostly due to the delay in reaching an accurate diagnosis and natural refractoriness to common forms of oncologic treatment (3).

Portal hypertension has a multifactorial aetiology in which there are numerous environmental and occupational carcinogens that are causative in the pathogenesis. The longest tracked profile of chemical risk is based around exposure to vinyl chloride monomer, thorium dioxide (Theorist), arsenic and anabolic steroids (4). These types of compounds have their mutagenic action through different processes: direct mutation of DNA, oxidative stress and chronic liver inflammation (5). The condition is increasingly supported by epidemiological links to a causal relationship with some traditional herbal medicines, in particular medicines containing aristolochic acid (6). Those who are exposed to such agents either via contaminated herbal drugs or accidental exposure to the environment reflect a significantly heightened propensity to portal hypertension and the development of other hepatoxic -malignancies. Thus, industrial chemicals as well as traditional medical practices jointly contributes to increasing the population risk (7).

The naturally occurring compound is a group of aristolochic acids (AA), particularly of the so-called Asian type of Aristolochic and Asarum species used in folk medicine and herbal medicines in parts of Asia and Eastern Europe. Botanical agents are commonly inculcated in weight-loss product, rheumatologic therapeutic products, in addition to various medicines (8). After gastrointestinal absorption, AA is metabolically activated by hepatic and renal cytochrome P450 enzymes to very electrophilic products that apparently can bind covalently to DNA and form mutagenic adducts. Aristolactam-mediated DNA adducts produced by the metabolic process are arising preferentially, the distinct phenomena related to AT-to-TA transversion mutations. A solid epidemiological and experimental evidence proves the carcinogenic nature of AA that leads to increased risks of developing urothelial carcinoma, chronic kidney disease, and hepatic angiosarcoma (9). Regulatory bodies in many countries have and continue to post formal warnings and ultimate restrictions, but these measures have not completely eliminated the residual exposure to people who use++ untested or otherwise improperly marked herbal preparations (10).

Table1 represents hepatic angiosarcoma has a close association with a number of already known environmental and occupational risk factors. The greatest correlation is with exposure to vinyl chloride, especially among the workers

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engaged in the production of PVC, where the long-term exposure favors mutagenic hepatic damage. Theorist (thorium dioxide) is another main risk factor, and this is a radiographic contrast agent that was used in the past which is not eliminated by the liver (after decades) and causes radiation-related carcinogenic (11). Another risk factor that poses threats to an individual as a result of arsenic exposure is in the production of pesticides or smelting of metals where chronic hepatic toxicity is formed. Other factors are chronic liver disease and cirrhosis that provide an inflammatory environment that promotes the development of tumors. All of these highlight a trend of progressive chemical, toxic, and inflammatory injuries which predispose people to hepatic angiosarcoma (12).

**Table 1:** Known Risk Factors of Hepatic Angiosarcoma

| Sr. No. | Risk Factor | Description | Estimated Incidence Rate or Prevalence | References |
|---|---|---|---|---|
| 1 | Vinyl chloride monomer | Industrial chemical used in plastics manufacturing; key occupational hazard | Major known cause; ~25% of cases with known cause | (13) |
| 2 | Arsenic | Environmental/occupational exposure; present in pesticides and contaminated water | Recognized but less common, due to regulation | (14) |
| 3 | Thorium dioxide | Formerly used radiographic contrast agent; discontinued | Historical cases; now essentially eliminated | (15) |
| 4 | Anabolic steroids | Used therapeutically or non-medically | Rare but established association | (16) |
| 5 | Oral contraceptives | Prolonged hormonal medication use | Possible but rare link | (17) |
| 6 | Radiation exposure | Prior medical radiation therapy | Uncommon risk factor | (18) |
| 7 | Herbal medicines (aristolochic acid) | Aristolochic/Asarum plants in traditional Asian remedies | Increasingly recognized; prevalence unknown | (19) |

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| | | | | |
|---|---|---|---|---|
| 8 | Genetic conditions | Neurofibromatosis type 1, hemochromatosis | Sporadic familial cases | (20) |
| 9 | Unknown etiology | No identifiable risk factor; spontaneous occurrence | ~75% of cases | (21) |

## 2. Aristolochic Acid Carcinogenesis and Mutational Signatures

### 2.1 Biochemical Pathways of Aristolochic Acid Activation and DNA Adduct Formation

AA is a highly toxic nephrotoxin and human carcinogen, which is rich in Aristolochic and Asarum species. During absorption, AA is activated by metabolism through the hepatic and renal xenobiotics processes and includes cytochrome P450 oxidases and xanthine oxidase. The major factor that determines the degree of AA toxicity is the conversion that entails conversion of AA to N hydroxy aristo lactam (HA) after refusal of the proton to generate the electrophilic nitrenium ion. Due to its extreme reactivity, this species covalently reacts with the nucleophilic N-6 of adenine to eventually form Aristolactam-DNA adducts (22). These adducts, especially the dA-ALI type, alter the helicity of the DNA, thus, making it difficult to replicate in an average manner and repair itself. Mutagenic and carcinogenic activity of AA is associated with this mechanistic pathway established in conjunction with photolabeling assays and advanced chromatographic techniques in vivo studies, as well as in vitro (23). Keystone urinary metabolite experimental data also suggests the urinary metabolite, Aristolactam I (ALI), becomes concentrated in renal tissues and still has high levels of adduct forming potential, so therefore, it is suggested to be a key contributor to AA mediated toxicity. The free-radical processes in adduct formation were also clarified to exhibit a relationship between these reactive species and site specific adducts with tumorigenesis (24).

### 2.2 Hallmark Mutational Signatures (A: T→T: A Transversions) and Comparison to Other Carcinogens

An unusual mutagenic phenotype of the mutant acids is a high number of A: T to T: A transversions, typical of the mutant acids. This characteristic signature can be explained by the fact that after the adduct is formed on adenine DNA, it leads to the misincorporation of adenine which causes the replacement of the A: T base pairs with T: A The resulting transversions are especially frequent at particular sequence motifs, and have no transcribed strand bias, especially at T/CA. When compared to other carcinogens, AA differs with other agents by being specific, that is, showing an absolute reliance on the A:T -T: A transversions (25). The strength of this mutational signature lies in the

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fact that it can be used as a diagnostic signature due to the high possibility of such an occurrence in the genome of a tumour indicating attempted AA exposure before. This type of traceability allows etiological connection between the environmental carcinogenesis and specified genetic consequences. These signature transversions are the most abundant mutations in the mutational spectrum in tumours created as a result of AA exposure, such as urothelial carcinomas and liver angiosarcomas, which establish AA-induced malignancy apart (26).

### 2.3 Methods for Detecting Mutational Signatures: Whole-Genome Sequencing and Bioinformatics Pipelines

One of the characteristics of mutant acids is the strongly increased level of AT to TA transversions that form another characteristic of mutant acids signature that can be used as a discrimination mutagen. This signature is based upon the molecular pathway comprising the creation of adenine DNA adducts which lead to the extension of the lifetime of the newly formed adduct, further raising probability of adenine misincorporation during future DNA replication and thus the replacement of AT base pairs with TA (27). T/CAG Such transversions have defined sequence positions preferences, preferentially no transcribed strand-biased. Comparatively, AA is unique in that it is highly selective: the only transversion that it causes is the AT-to-TA (28). This attribute gives diagnostic value since the occurrence of the signature in tumors genomes is used to determine an association to the AA exposure in the past, and it enables a valuable tissue-specific correlation of environmental carcinogenesis (external factor) and genetic events. The existence of AA-mediated TA transversions represents the most prevalent mutation type in AA-induced tumors-urothelial carcinomas and liver angiosarcomas thus defining AA-specific tumors (29).

### 2.4 Aristolochic Acid Signature in Human Cancers

There are a number of landmark studies identifying the diagnostic utility of the aristolochic acid mutational signature. Such A:T C N:G T:A transversions represent a prominent pattern throughout tumour genomes in patients with urothelial carcinomas of the upper urinary tract due to exposure to a variety of herbal medicines that have aristolochic acid as a common constituent (30). Comparative investigation of primary hepatic angiosarcoma samples, especially those that have reported history of environmental or herbal exposure, give positive confirmation to the signature of aristolochic acid formation of mutations (31). These tumours have been structurally identified which has enabled them to conduct targeted Eito pathological study and advocacy for strict regulation of aristolochic acid products in the international market. All these studies exemplify how molecular epidemiology carries the potential of transforming in the discovery of the carcinogenic effects of environmental exposures (32).

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Table 2 represents Comparison of mutational patterns induced by AA and mutational patterns induced by other major hepatotoxins shows different patterns. A characteristic pattern of A:T→T:A transversion and a strong enrichment of COSMIC Signature SBS22, which is evidence of bulky DNA adducts and impaired DNA repair, characterize AA (33). On the other hand, hepatotoxins like aflatoxin B1 mainly cause G:C T: A transversion related to SBS24 when they are exposed but exposure to vinyl chloride produces SBS4-like transpositions that can be attributed to the formation of ethion-DNA adducts. Alcohol-hepatic injury is also typified by mutation patterns that are attributable to oxidative damage, mostly C: G: A: T changes. Arsenic and thorium dioxide exposure result in more diffuse and less specific signatures, which is probably caused by chronic inflammation and radiological effects (34).

**Table 2:** Catalog of Mutational Signatures Associated with Aristolochic Acid Versus Other Hepatotoxins

| Sr. No. | Mutational Signature | Key Mutation Pattern | Sequence Context Preference | Associated Hepatotoxin | Characteristic Features and Notes | References |
|---|---|---|---|---|---|---|
| 1 | SBS22 (COSMIC) | A: T → T: A transversions (dominant) | Predominantly occurs at T/CAG trinucleotide motif | Aristolochic Acid (AA) | Unique and robust AA signature; strong bias to no transcribed DNA strand; linked to AA exposure in hepatic and urothelial cancers. | (35) |
| 2 | Aflatoxin B1 Signature | G:C → T: A transversions | G at mutation site | Aflatoxin B1 (aflatoxin) | Common in hepatocellular carcinoma; causes mutagenesis via guanine adducts. | (36) |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Distinct from AA pattern. | |
| 3 | Vinyl Chloride | Multifocal mutations, including G → A transitions | Varied | Vinyl chloride | Linked to hepatic angiosarcoma; lacks singular dominant transversion pattern compared to AA signature. | (37) |
| 4 | Benzo[a]pyrene | G:C → T: A transversions | Guanine sites | Benzo[a]pyrene (tobacco smoke) | Frequent in lung cancers; differs notably from AA's A: T→T: A transversions. | (38) |
| 5 | UV Radiation | C → T transitions | Dipyridine sequences | Ultraviolet radiation | Typical in skin cancers; distinctly different from AA mutational patterns. | (39) |

## 3. Genomic Landscape of

## Primary Hepatic Angiosarcoma

### 3.1 Overview of Genomic Alterations in Angiosarcoma Subtypes

Angiosarcomas (AS) are a small group of vascular tumours with an aggressive behaviour characterised by high genomic heterogeneity which depends on anatomic location and aetiology. The common recurrent genetic aberrations are mutations in tumour suppressor gene TP53 which have been found in an estimated range of 30-38 % of tumours, and have been involved in genomic instability and progression of tumours (40). Other commonly mutated genes include POT1, which are involved in telomere maintenance as well as

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genes which are involved in chromatin remodelling; examples include chromatin remodelling gene, ARID1A (41). MYC oncogene amplification is common in radiation-related angiosarcomas and in breast-related ones especially, angiogenesis regulator mutations like KDR (VEGFR2) and FLT4 are site-specific. Other mutations in drivers act on the signalling pathways such as PI3K/AKT and RAS families more so at reduced rates. Genomic landscape further varies as a result of structural changes, such as gene fusions of PLCG1 and CRKL. There is also genomic disparity between subtypes e.g. head and neck versus breast AS, which indicates differences in pathogenic mechanisms and clinical behaviours, and warrants the use of a bespoke molecular characterisation at the base of precision therapies (42).

### 3.2 Comparative Analysis: Genomic Data from Smaller Angiosarcoma Cohorts

Angiosarcoma-specific cohorts of smaller size provide more detailed analysis, which is constrained by its size. Recurrent mutations in TP53, MYC, CDKN2A and tyrosine kinase receptor genes emerge as evidenced by TCGA-level data, although the average mutation burdens of the latter are poorer than those of the targeted cohorts (43). The smaller series demonstrate significantly elevated TMB, and a higher rate of mutational heterogeneity, which is partly supported by anatomical distribution and pre-existing exposure to radiation. Such angiosarcomas as head-and-neck, for instance, have a strikingly high TMB with very common POT1 mutations that are absent in other cohorts (44). On the contrary, breast angiosarcomas exhibit increased frequencies of MYC amplification and have a history of prior radiation in the majority of cases. This synthesized data supports not only the significant numerical heterogeneity of angiosarcoma, but also highlights the need of the clinical trial designs and treatment strategies to consider the anatomic and molecular subtypes to maximize outcomes of therapeutics (45).

### 3.3 Evidence for Aristolochic Acid–Specific Mutations in Hepatic Angiosarcoma

Primary hepatic angiosarcomas caused by aristolochic acids have a characteristic mutational signature of A:T T: A transversions that is often seen in liver specimens of whole-genome sequencing of patients with contact exposure to aristolochic acid and in patients with documented or suspected exposure (46). They are additive at selective trinucleotide motifs with strong strand direction and therefore have become a molecular fingerprint to help distinguish distinctly aristolochic-acid-induced tumours as compared to tumours driven through other carcinogens like vinyl chloride or aflatoxin B1. Detection of these classic mutations is supplemented by other mutational patterns of chronic DNA damage and adduct formation and this further provides etiologic support giving credence to the postulated carcinogenic effects of aristolochic acid .These perspectives hold valuable consequences to epidemiologic surveillance, risk stratification, and possibly to the mode used to make decisions

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about the treatment since they allow the use of chemically induced subtypes of hepatic vascular cancer (47).

### 3.4 Integration of Mutational Signature Data with Copy-Number Alterations and Structural Variants

A genomic study that thoroughly characterises hepatic angiosarcoma provides convincing evidence that AA mutational signatures are present with other genetic and insertional or deletional segments, causing a complex genetic profile. The most noticeable CNAs are amplifications of oncogenes (mainly MYC) seen in 20]25 % of tumours, and deletions of tumour suppressors (mainly CDKN2A), which derail cell-cycle control (48). Structural variants, such as gene fusions (fusion of ROS1 with GOPC), add other oncogenic drivers and can potentially impact tumour behaviour and clinical behaviour. The combination of AA specific mutational profiles with these genomically aberrant processes suggests a two-part carcinogenic response where the AA exposure can promote both the small scale (point mutational) error as well as large scale (chromosomal) errors. This integrative genomic structure enhances molecular stratification with a highlight of many levels of tumour-driving processes, thus giving an option of combination therapies and precision oncology treatments (49).

Figure 1 represents the distributions of trinucleotide mutation motifs in several different specimens, and each single cell represents the relative frequency or enrichment of a specific motif in a specific specimen. The colour gradient used runs between blue, which is representing lower frequency or depletion, to orange-red, which is representing higher frequency or enrichment hence allowing quick visual comparison of mutational patterns (50). The fact that there is a strong diagonal shift of blue towards orange suggests progressive enrichment of the motifs in certain groups of specimens. It has localized red hotspots, which is indicative of the motifs that are extremely represented in specific samples (51). The general direction draws attention to the high level of heterogeneity between specimens, which, in turn, implies the existence of different mutational dynamics or external influences. The continuum of hues also suggests that there has been a clustering or a similarity in adjacent specimens. As such, the given visualization is useful in identifying signature-like patterns and in explaining possible biological factors behind motif distributions (52)

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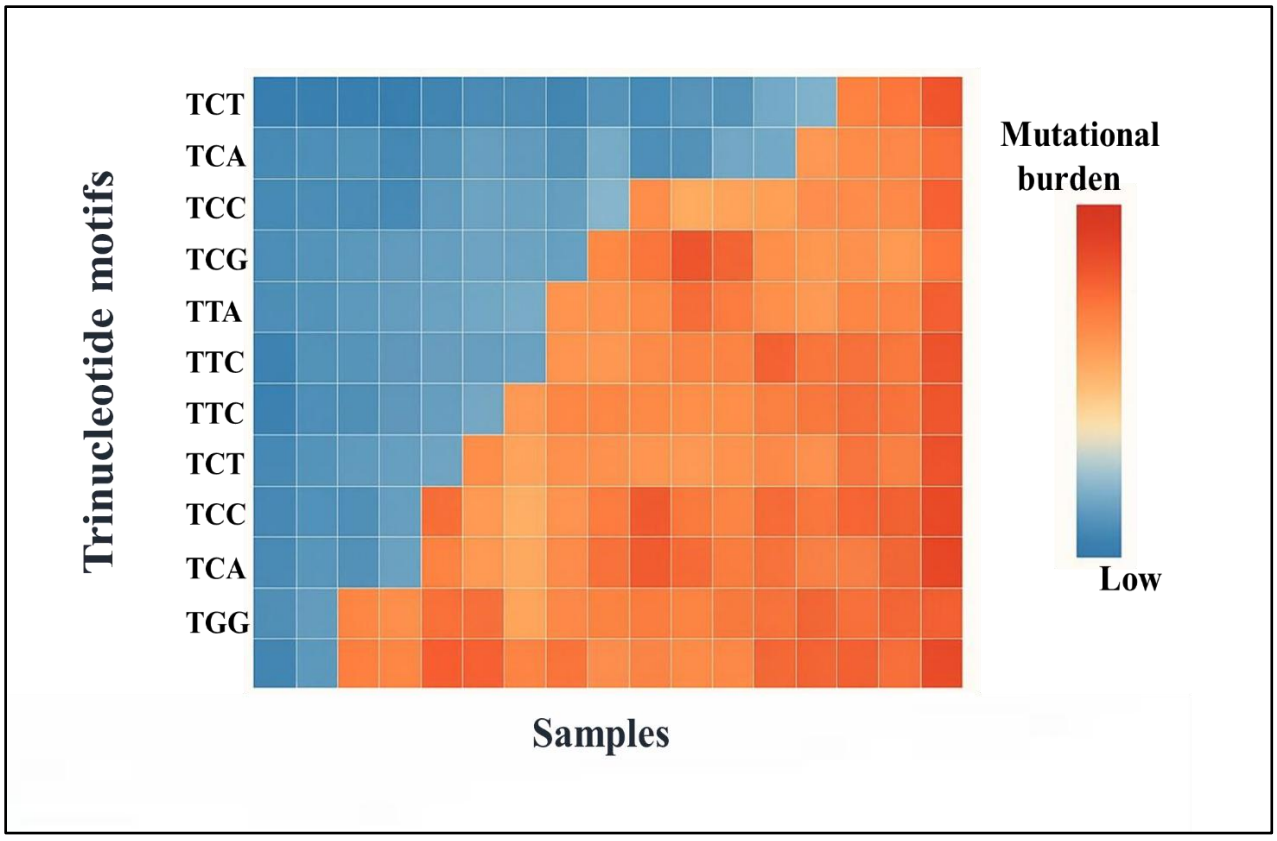


**Figure 1.** Heatmap of mutational burdens across angiosarcoma samples

*The male colour bar at the right of the image shows the legend in this heatmap. It shows a gradual transition of deep blue which is shown at the bottom up to light blue, then to light orange, and lastly, deep orange-red in the apex. The gradient indicates the relative values that are represented in the cells of the heatmap-blue areas have a lower value, and areas with orange and red colour will have a higher value. The legend thus helps in defining the comparative significance of each motif in each sample in terms of the intensity of coloration.*

## 4. Identification of Novel Biomarkers

### 4.1 Proteomic and Transcriptomic Profiling Approaches

Proteomic and transcriptomic profiling is a very important research technique related to the understanding of the molecular pathogenesis of PHA and biological impact of the exposure to AA. Proteomics uses mass spectrometry

ISSN: 3093-4737

methodologies to measure the total repertoire of proteins produced in tumour cells and tissues, enabling the detection of protein expression and/or post-translational modifications of those proteins that are aberrantly regulated or involved in tumorigenesis, angiogenesis or multidrug resistance (53). Combined with high-resolution tandem mass spectrometry, label-free quantitation and isotope labelling approaches can be used to identify the presence of differentially expressed proteins in PHA as compared to normal hepatic or other sarcomas. Transcriptomics, of RNA sequencing (RNA-seq) or microarrays can be used to measure expression profiles of mRNA to help decipher dysregulated gene networks, signalling pathways, and non-coding RNA signatures associated with the biology of the tumours and AA exposures(54). The advantages postulated by single-cell RNA-seq are that it further refines this analysis by solving heterogeneity of the cellular make-up of the tumour microenvironment. Combination of proteomic and transcriptomic data provides complementary information on gene-expression control and functional protein products thus presenting candidate biomarkers of diagnosis, prognosis and therapeutic targeting in hepatic angiosarcoma (55).

### 4.2 Candidate Biomarkers Linked to Aristolochic Acid Exposure

The proteins that have been suggested as candidate biomarkers in association with exposure AA in the liver angiosarcoma are mainly linked to the pathways of DNA damage and repair, regulation of oxidative stress, and regulation of apoptosis. It is worth noting that the aberrations touched on the tumour suppressor pathway of p53, since p53 is pivotal in the actions of the cell to the DNA adducts produced by AA metabolites. Genomic integrity and aggressive tumours are associated with mutation and abnormal expression of p53 (56). Enzymes involved in repairing the DNA including ERCC1 and FANCD2 reflect attempts by cellular processes to overcome AA-induced damage to the DNA as they are expressed differently in tumour cells exposed to AA. The increased expression of nucleotide excision repair protein could be considered not only the sign of protective response but also of mutagenic load (57). There is also increased levels of indicators of oxidative stress such as glutathione S-transferases and superoxide dismutase. Ki-67 proliferation index also reports on the levels of tumour aggressiveness. The combination of these candidate biomarkers offers functional annotations to AA-mediated mutagenesis, tumour vascularity, and cellular proliferation, and therefore, combining these biomarkers into diagnostic and prognostic panels would develop a justification (58).

### 4.3 Validation Strategies: Immunohistochemistry, Serum Assays, and Cell-Free DNA Analysis

Strict validation process of biomarkers in hepatic angiosarcoma requires a collection of concomitant solutions. Immunohistochemistry (IHC) retains a primary role, allowing protein targets to be spatially and cellularly localized, the

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extent of expression and distribution pattern to be determined in ERG, p53, and DNA repair enzymes, and to relate to histopathology and clinical outcomes (59).At the same time, serum-based tests that enable the non-invasive measurement of proteins present within a blood circulation volume. It envisions the use of such assays in early detection, therapy monitoring and prognostication use. More sensitive methods, in particular the presence of cell-free DNA (cfDNA) in plasma or serum, allow identifying the genetic changes associated with the tumour including mutational signatures of angiosarcoma. Next-generation cfDNA sequencing provides real time, minimally invasive biomarker readouts, monitoring of disease dynamics, and personalized medicine applications (60).

### 4.4 Biomarker Panel Development and Performance Metrics

Having an effective biomarker panel is one that is optimized to improve the diagnosis sensitivity, specificity, and prognosis to stan out the aristolochic acid-related hepatic angiosarcoma. The apt combination of molecular markers would be required to enhance the collective individual characteristics of markers. Some of the common components are endothelial markers (e.g., ERG, CD31), repair of DNA (e.g., ERCC1), tumour suppressors (e.g., p53) and proliferating indices (e.g., Ki-67) (61). Combining the information contained in protein expressions with mutational signatures extends the business of clinical decision making. Performance measures are measured using prospective validation studies, and these include sensitivity, specificity, positive predictive value, and negative predictive value (62). Determination of the best thresholds of biomarkers and panel ensemble is done using receiver operating characteristic curve analysis. A good panel of biomarkers should balance thorough capture of tumor attributes with real-life factors, in the form of assay reproducibility and cost, and earlier tumor assessment, risk assessment and personalized targeting, in PHA (63).

Table 3 represents the most important candidate biomarkers of hepatic angiosarcoma, including the summary of their roles and routes of detection. The basic biomarkers, i.e., p53, ERG, and KDR/VEGFR2 are emphasized because of their subsequent contributions to the genomic instability, endothelial identity, and angiogenic signalling (64). The tracing of the etiology of toxin-associated exposure is done using exposure-associated markers such as aristolochic acid-derived DNA adducts. A group of circulant proteins and inflammatory mediators have been observed to have an ability to reflect vascular damage and tumour evolution. Additional diagnostic information is that of epigenetic changes, especially the change in DNA methylation (65).

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**Table 3:** List of Candidate Biomarkers with Functional Annotations and Detection Methods

| Sr. No. | Biomarker | Functional Role | Association with AA Exposure | Detection Method(s) | References |
|---|---|---|---|---|---|
| 1 | ERG (Transcription factor) | Endothelial cell differentiation; angiogenesis regulation | Highly specific for hepatic angiosarcoma | Immunohistochemistry (IHC) | (66) |
| 2 | p53 (Tumor suppressor) | DNA damage response, cell cycle arrest | Frequently mutated/altered in AA-induced tumors | IHC, cfDNA sequencing | (67) |
| 3 | ERCC1 (DNA repair enzyme) | Nucleotide excision repair | Upregulated in response to AA-induced DNA adducts | IHC, serum assays | (68) |
| 4 | FANCD2 (DNA repair) | Interstrand crosslink repair | Altered expression linked to AA exposure | IHC, transcriptomic profiling | (69) |
| 5 | Ki-67 (Proliferation marker) | Cellular proliferation | Correlates with tumor aggressiveness | IHC | (70) |
| 6 | Glutathione S-transferase | Antioxidant defense | Elevated in response to oxidative stress from AA | Serum assays, proteomics | (71) |

Figure 2 represents the schematic outlines a streamlined workflow that will hasten precision oncology efforts to be achieved within the frame of rare oncological conditions like hepatic angiosarcoma.The resulting data are then included in the stage of bioinformatic analysis that involves mutational signature

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profiling, differential expression, pathway interrogation, and the discovery of putative novel biomarkers (72). The hypothetical biomarkers are then tested in a validation cohort by the use of independent samples of the patient by the use of targeted sequencing, immunohistochemical and functional assays to support the biological relevance. Finally, the validated biomarkers are incorporated into the clinical practice, which supports the creation of diagnostic panels, therapeutic targeting strategies and personalized treatment regimes (73).

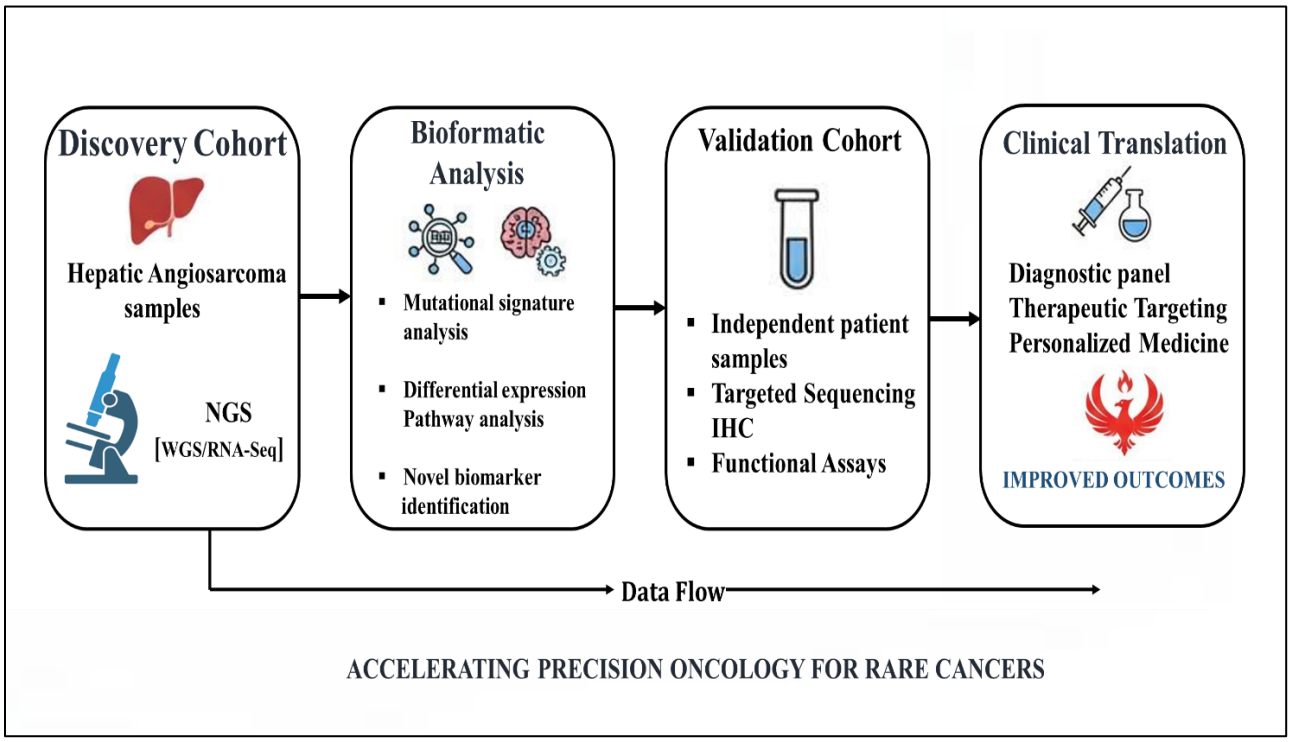


**Figure 2.** Workflow for biomarker discovery and validation in hepatic angiosarcoma

*The character does not have a typical legend instead; he has a series of pictorial signals used to denote each step of the methodology visually. The liver and microscope icons are used as the representation of hepatic angiosarcoma specimens and next-generation sequencing respectively. The bioinformatic stage where mutational signature analysis, pathway reconstruction, biomarker identification are carried out are referred to as gears, molecular network motifs, and a stylised brain therapeutic use and is marked with the terminal clinical translation node, and a phoenix motif represents the expected improvement of patient outcomes. All these icons, together, form a combined, image-based mythology, which makes it easy to interpret the workflow.*

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5.

## Functional Characterization of Biomarkers

### 5.1 Primary Cells, Organoids, and Cell Lines

The one outstanding model that has been critical in mechanistic study of primary hepatic angiosarcoma is the in vitro models. Such systems allow a systematic search to identify cellular responses to the exposure of aristolochic acids and allow a quantitative analysis of candidate biomarkers (74). Well-characterized angiosarcoma cell line models genetically engineered to stably express mutant p53 or DNA repair deficiencies are scalable models to enable massively parallel drug screening, genetic perturbation, and pathway interrogation. Enable the derivation of phenotype based on a potential biomarker and form the basis of translation directed toward development of specific therapeutics (75).

### 5.2 Patient-Derived Xenografts and Genetically Engineered Mice

The use of in vivo model is an irreducible step in genuine in vitro hypothesis confirmation and in clarifying the pathophysiological consequences of AA related mutagenesis of hepatic angiosarcoma. These models represent a faithful recapitulation of the natural history of disease progression, metastatic tendency and response to therapy and are thus prior to pre-clinical testing (76). To enable the mechanistic study of carcinogen-induced transformation, genetically engineered mouse models, made to express AA signature mutations participate in DNA damage response and tumor microenvironment interactions. These models unravel the complicated intercommunication between genomic changes to the surrounding, environmental exposure, and tumour evolution hastening the process of translation of the biomarker based research into clinical practice (77).

### 5.3 Functional Assays: Proliferation, Invasion, and DNA Damage Response

The methods of functional assays form the foundation of investigating the biologic effects of exposure to (AA) and determining the usefulness of biomarker candidates. Proliferation assays are based on colorimetric (MTT) or fluorescence (Edu incorporation) readout and measure the cell growth (proliferation) within simplistic biomarker-positive versus biomarker-negative subpopulations (78). The aspect of DNA damage response is interrogated using γ-H2AX foci formation, comet assays or by quantifying double-strand break repair kinetics and this process provides crucial insight on the functional to conclude the real important product of AA-induced mutagenesis-damage to genomic stability. Such combination of the functional endpoints provides strong phenotypic characterization, insights into the disease mechanism through a more comprehensive understanding of disease etiology, and enables the rationalization of drug-

ISSN: 3093-4737

screening approaches against vulnerabilities in AA (79).

### 5.4 Correlation of Biomarker Expression with Clinical Outcomes and Aristolochic Acid Exposure Histories

The usefulness of candidate biomarkers in hepatic angiosarcoma is subject to their correlation to patient outcomes being validated and to reported personal exposure histories of AA Retrospective and prospective cohort studies use immunohistochemistry, serum assays, and the cell-free DNA profile to measure patient population-based biomarker expression in well-characterized patient populations. Statistical approaches, in particular Kaplan Meier survival analysis and Cox proportional hazards regression, define the relationships between biomarker level (80). Etiologic relevance is supported by stratifying by an AA exposure history and generating subgroup identifiers of high- and low-risk groups, and refining prognostic precision. Personalized medicine practices are in turn informed by integrative biomarker analysis to design surveillance formats, treatment choices, and risk-based mode of hepatic angiosarcoma management among the AA-exposed population (81).

## 6. Therapeutic Implications and Targeted Strategies

The treatment of hepatic angiosarcoma is currently being approached using therapeutic approaches which are more dependent on the identification of particular molecular targets to improve the treatment process. Important signalling pathways, such as VEGF/VEGFR and PI3K/Akt offer prospects to medical creation of specific anti-angiogenic reagents and kinase inhibitors (82). Responsible changes in p53 and DNA repair indicate that agents which enhance apoptosis or take advantage of repair defects can incur some extra therapeutic advantages. Biomarker-based selection would have the potential to enhance the effectiveness of immunotherapy in chosen groups of patients (83).

### 6.1 Targeting DNA Repair Pathways Dysregulated by Aristolochic Acid

Bulky DNA adducts associated with severe genomic instability are acquired following stimulation by AA, which blocks and dysregulates the DNA repair pathways, especially the nucleotide excision repair pathway and the homologous recombination pathway (84). A key paradigmatic approach to therapy is the inhibition of poly-(ADP-ribose) polymerase (PARP), which plays a key role in the repair of single-strand breaks of DNA and the orchestration of the general response to cellular DNA damage. PARP inhibitors (PARPi), including olaparib, niraparib and rucaparib, act by inhibiting fixing of simple breaks, thus causing the formation of deadly multiple bouton breaks and apoptosis in the cells (85). As sensitivity to PARP inhibition has proven remarkable in preclinical and clinical studies, tumors with BRCA1/2 mutations or more general homologous recombination deficiencies. PARPi is a logical and effective class of DNA repair deficit treatment in AA and has a potential

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to customize that to individual treatment based on biomarker-personalized choices (86).

### 6.2 Small-Molecule Inhibitors and Monoclonal Antibodies Against Novel Biomarkers

The shift in therapeutic approaches has now involved the paradigm into not only repairing the DNA but to also disrupt key biomarkers that define angiosarcoma developing in response to exposures of acrylonitrile (87). At the same time, there is an increased molecular specificity offered by monoclonal antibodies as primary targets, which are vascular (CD31, ERG, VEGF) and immune checkpoint regulators (PD-1, PD-L1). These developments in the sphere of biomarker-guided treatment regimens can be seen as the shift towards the new paradigm of individualized treatment based on pathogenic specificity of the acrylonitrile-induced angiosarcomas that could potentially overcome the traditional chemoresistance (88).

### 6.3 Combination Therapies: Integrating Biomarker-Guided Approaches with Existing Chemotherapeutics

Studies on the molecular and genetic triggers of AA caused by aniline dye chemical compounds revealed that these stimuli produce complex genomic and epigenomic changes, which seem to make monotherapy virtually incapable of exerting a far-reaching clinical impact (89). The particular mechanistic synergies that rational drug combinations exploit fall into 3 categories:

(1) PARP inhibitors increase the sensitivity of DNA repair-deficient cells to DNA-damaging chemotherapies

(2) antiangiogenic agents undermine endothelial integrity and permit augmented delivery of cytotoxic drugs

(3) Immunotherapeutics sometimes can induce a modulating immune recognition and effector response against genomically labile tumor cells (90).

### 6.4 Preclinical Efficacy and Safety Data

The efficacy of various, targeted agents, namely poly (ADP-ribose) polymerase (PARPs), tyrosine kinase inhibitor, and monoclonal antibodies, have been consistently detected using preclinical models to target angiosarcoma that occur in alcohol-associated livers (91). It has been empirically found that a combination regimen has shown an antitumor effect that is additive and/or synergistic without any augmentation of organ toxicity, broadening therapeutic windows. Along with these findings, the existing clinical translation and optimization of targeted therapies against angiosarcoma based on alcohol-related liver disease has an effective foundation (92).

## 7. Future prospects

A coherent model of the design of a biomarker-guided clinical trial in hepatic angiosarcoma should be developed due to its scarcity and heterogeneity by molecular parameters. Stratification of patients should go beyond the conventional clinical characteristics and include

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molecular characteristics like p53 status mutation, expression of ERG, and aristolochic acid related mutational signature (93). Basket and umbrella trials Adaptive trial designs can be used to efficiently test a specific set of targeted therapies in subgroups with molecular characteristics. Outcome measures ought to combine the traditional oncological outcomes, including overall and progression-free survival, and dynamic biomarker-based variables. Real-time pharmacodynamic and mechanistic analyses of tumor tissue and liquid biopsy samples may be achieved by early procurement (94). The effectiveness of regulatory measures must be based on strict analytical validation of companion diagnostics to be accurate, reproducible and clinically relevant, preferably co-developed with therapeutic agents. Multi-institutional and international partnerships are essential considering that due to the complexity of the tumor heterogeneity and scarcity of patients, it is essential to improve the statistical power and the ability of the trial to proceed (95). The new technologies such as liquid biopsy, single-cell sequencing, and AI-driven genomic analytics have a transformative potential of accurate patient stratification, exposure assessment and prediction modeling, marking a new era of precision oncology of hepatic angiosarcoma (96).

## 8. Conclusion

AA chronic exposure was associated with the formation of urothelial and hepatic malignancies with the ensuing mutational signatory, an increase of A: T to T: A transversion, providing an absolute diagnostic indicator of exposure. The pattern occurs most strongly in particular genomic motifs and is a stable molecular fingerprint, permitting retrospective evaluation of environmental carcinogen exposure, which can explain specific genetic effects of exposure to AA. New biomarkers discoveries have disclosed new molecular targets, like defective pathway of p53, mis regulated DNA repair enzymes, and endothelial biomarkers, like ERG. These biomarkers allow more personalized diagnostic algorithm, prognostication, and the logical development of specific targeted therapies not the least of which is the PARP inhibitors and angiogenesis inhibitors made to order with respect to the molecular basis of the carcinoma. The future may lead to the dominance of precision medicine in rare chemically induced cancers, as current attempts to integrate the next generations of technologies, such as the liquid biopsy, single-cell sequencing, and AI-based analysis of mutation data will shape the adoption period of better detection of the disease and personalized treatment interventions leading to significantly higher clinical outcomes and lower oncology-related morbidities in the patient population that has been historically underserved by conventional approaches.

## SUMMARY

The current review outlines the mechanism through which exposure to Aristolochic Acid (AA) induces characteristic mutational signals, which are at the centre of the oncogenesis of primary hepatic angiosarcoma. It is based on the

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combination of genomic, transcriptomic, and biomarker-discovery data and the elucidation of altered molecular pathways induced by AA-induced DNA damage. The paper highlights the newly discovered biomarkers of diagnostic, prognostic and treatment importance. Furthermore, it describes the possible use of these biomarkers to inform accuracy therapeutic plans and improve clinical outcomes of this rare and aggressive malignancy.

**References**


1. Aung ZZ. A STUDY ON THE BENEFITS AND COSTS OF MANGO FARMING (CASE STUDY: THA PYAY YOE VILLAGE, SINT GAING TOWNSHIP) (Zaw Zaw Aung, 2024): MERAL Portal; 2024.

2. Al-zubaidi HB, Rusin AV. Cancer emergencies and paraneoplastic syndromes. 2023.

3. Mutala TM. Oncologic surgical complications: Imaging approach and characteristics. European Journal of Radiology. 2024:111876.

4. Thakur S, Chandra A, Kumar V, Bharti S. Environmental pollutants: endocrine disruptors/pesticides/reactive dyes and inorganic toxic compounds metals, radionuclides, and metalloids and their impact on the ecosystem. Biotechnology for environmental sustainability: Springer; 2025. p. 55-100.

5. Di Carlo E, Sorrentino C. Oxidative stress and age-related tumors. Antioxidants. 2024;13(9):1109.

6. Yang L, Lin W, Shi M, Huang Z, Zhang X, Yang Y, et al. Whether aristolochic acid directly drives hepatocarcinogenesis: comprehensive investigations from mutational signatures to animal models. Archives of Toxicology. 2025:1-12.

7. Zhou W, Li M, Achal V. A comprehensive review on environmental and human health impacts of chemical pesticide usage. Emerging Contaminants. 2025;11(1):100410.

8. Paul AK, Jahan R, Paul A, Mahboob T, Bondhon TA, Jannat K, et al. The role of medicinal and aromatic plants against obesity and arthritis: a review. Nutrients. 2022;14(5):985.

9. Abrignani MG, Lucà F, Abrignani V, Nucara M, Grosseto D, Lestuzzi C, et al. Risk Factors and Prevention of Cancer and CVDs: A Chicken and Egg Situation. Journal of Clinical Medicine. 2025;14(9):3083.

10. Taylor M. Whither the Regulator: Food and Drug Law, the Natural Health Product Regulations and the Erosion of Safety, Efficacy and Quality. 2024.

11. Singer LT, Schumacher F, Fabisiak J, Dietz LJ, Ciesielski T. The East Palestine train derailment: A complex environmental disaster. Neurotoxicology and Teratology. 2025:107522.

ISSN: 3093-4737

12. Teschke R. Copper, iron, cadmium, and arsenic, all generated in the universe: Elucidating their environmental impact risk on human health including clinical liver injury. International journal of molecular sciences. 2024;25(12):6662.

13. Edo GI, Ndudi W, Ali AB, Yousif E, Zainulabdeen K, Onyibe PN, et al. Poly (vinyl chloride)(PVC): an updated review of its properties, polymerization, modification, recycling, and applications. Journal of Materials Science. 2024;59(47):21605-48.

14. Luong HTT, Vercammen S, de Marco A, De Rooster H, Cosma A. Angiosarcoma: a systematic review of biomarkers in diagnosis, prognosis, and therapeutic strategies. Frontiers in Oncology. 2025;15:1623327.

15. Huang SC, Chang IYF, Chang CJ, Liu H, Chen KH, Liu TT, et al. Association between hepatic angiosarcoma and end-stage renal disease: nationwide population-based evidence and enriched mutational signature of aristolochic acid exposure. The Journal of Pathology. 2023;260(2):165-76.

16. Li C, Li X, Niu M, Xiao D, Luo Y, Wang Y, et al. Unveiling correlations between aristolochic acids and liver cancer: spatiotemporal heterogeneity phenomenon. Chinese Medicine. 2024;19(1):132.

17. Zhang Q, Chen J, He H, Zhao W, Wong Y, Li W, et al. Hepatotoxic effects of aristolochic acid: Mechanisms and implications. Acta Materia Medica. 2024;3(3):349-62.

18. Mukherjee B, Rajagopalan M, Chakraborty S, Ghosh P, Ray M, Sen R, et al. Hepatocellular carcinoma: diagnosis, molecular pathogenesis, biomarkers, and conventional therapy. Nanotherapeutics for the Treatment of Hepatocellular Carcinoma: Bentham Science Publishers; 2022. p. 1-97.

19. Ang LP, Ng PW, Lean YL, Kotra V, Kifli N, Goh HP, et al. Herbal products containing aristolochic acids: A call to revisit the context of safety. Journal of Herbal Medicine. 2021;28:100447.

20. Chen TW-W, Burns J, Jones RL, Huang PH. Optimal clinical management and the molecular biology of angiosarcomas. Cancers. 2020;12(11):3321.

21. Lai H-Y, Wu L-C, Kong P-H, Tsai H-H, Chen Y-T, Cheng Y-T, et al. High level of aristolochic acid detected with a unique genomic landscape predicts early UTUC onset after renal transplantation in Taiwan. Frontiers in Oncology. 2022;11:828314.

22. Manapkyzy D, Zhamanbayeva G, Sidorenko V, Bonala R, Johnson F, Matkarimov BT, et al. Thymines opposite to bulky aristolactam-DNA adducts in duplex DNA are not targeted by human thymine-DNA glycosylase. PeerJ. 2025;13:e19577.

23. Eisenbrand G. Revisiting the evidence for genotoxicity of acrylamide (AA), key to risk assessment of dietary AA exposure. Archives of toxicology. 2020;94(9):2939-50.

ISSN: 3093-4737

24. Lahiri M, Mukhtar H, Agarwal R. Reactive intermediates and skin cancer. Carcinogenicity: CRC Press; 2021. p. 679-714.

25. Siddiqui SI, Allehyani ES, Al-Harbi SA, Hasan Z, Abomuti MA, Rajor HK, et al. Investigation of Congo red toxicity towards different living organisms: a review. Processes. 2023;11(3):807.

26. D'Angelo A, Bagby S, Galli IC, Bortoletti C, Roviello G. Overview of the clinical use of erdafitinib as a treatment option for the metastatic urothelial carcinoma: where do we stand. Expert Review of Clinical Pharmacology. 2020;13(10):1139-46.

27. Behl T, Rachamalla M, Najda A, Sehgal A, Singh S, Sharma N, et al. Applications of adductomics in chemically induced adverse outcomes and major emphasis on DNA adductomics: a pathbreaking tool in biomedical research. International journal of molecular sciences. 2021;22(18):10141.

28. Hwa Yun B, Guo J, Bellamri M, Turesky RJ. DNA adducts: Formation, biological effects, and new biospecimens for mass spectrometric measurements in humans. Mass spectrometry reviews. 2020;39(1-2):55-82.

29. Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, et al. NCCN guidelines® insights: bladder cancer, version 2.2022: featured updates to the NCCN guidelines. Journal of the National Comprehensive Cancer Network. 2022;20(8):866-78.

30. Dickman KG, Chen C-H, Grollman AP, Pu Y-S. Aristolochic acid-containing Chinese herbal medicine and upper urinary tract urothelial carcinoma in Taiwan: a narrative review. World journal of urology. 2023;41(4):899-907.

31. Sidorenko VS. Biotransformation and toxicities of aristolochic acids. Mechanisms of Genome Protection and Repair. 2020:139-66.

32. VanEvery H, Franzosa EA, Nguyen LH, Huttenhower C. Microbiome epidemiology and association studies in human health. Nature Reviews Genetics. 2023;24(2):109-24.

33. Zhuravleva E, O'Rourke CJ, Andersen JB. Mutational signatures and processes in hepatobiliary cancers. Nature Reviews Gastroenterology & Hepatology. 2022;19(6):367-82.

34. Stoian IA-M, Vlad A, Gilca M, Dragos D. Modulation of Glutathione-S-Transferase by Phytochemicals: To Activate or Inhibit—That Is the Question. International Journal of Molecular Sciences. 2025;26(15):7202.

35. Villa M, Malighetti F, De Sano L, Villa AM, Cordani N, Aroldi A, et al. Comprehensive analysis of mutational processes across 20 000 adult and pediatric tumors. Nucleic Acids Research. 2025;53(13):gkaf648.

36. McGlynn KA, Watling CZ, Hernandez BY, Groopman JD. Environmental risk factors for liver cancer. Hepatology. 2025:10.1097.

ISSN: 3093-4737

37. Tessema ST, Mahgoub AE, Nakhleh R, Tessema S, Mahgoub A. Angiosarcoma: A Rare Malignancy Linked to Chemical Exposures. Cureus. 2022;14(5).38. Huang W-Y, Chen Y-F, Huang K-Y. The association between ambient air pollution exposure and connective tissue sarcoma risk: a nested case–control study using a nationwide population-based database. Environmental Science and Pollution Research. 2024;31(6):9078-90.

39. Ike E, Mai JZ, Sargen MR, Schonfeld SJ, Cahoon EK. Ambient UV radiation is associated with cutaneous angiosarcoma incidence in the United States, 1992 to 2020. Journal of the American Academy of Dermatology. 2024;91(1):102-4.

40. Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, et al. Mutant p53 in cancer: from molecular mechanism to therapeutic modulation. Cell death & disease. 2022;13(11):974.

41. Zade NH, Khattar E. POT1 mutations cause differential effects on telomere length leading to opposing disease phenotypes. Journal of Cellular Physiology. 2023;238(6):1237-55.

42. Kutasovic JR, McCart Reed AE, Sokolova A, Lakhani SR, Simpson PT. Morphologic and genomic heterogeneity in the evolution and progression of breast cancer. Cancers. 2020;12(4):848.

43. Sanchez AM, De Lauretis F, Bucaro A, Pirrottina CV, Borghesan N, Franco A, et al. Long term outcomes of breast primary sarcomas and malignant phyllodes tumors: 20 years observational analysis of the BEAM∗ study group.(∗ the breast European association for mesenchymal tumors). European Journal of Surgical Oncology. 2025;51(10):110265.

44. Espejo Freire A, Elliott A, Rosenberg A, Costa PA, Barreto-Coelho P, Jonczak E, et al. Genomic landscape of angiosarcoma: a targeted and immunotherapy biomarker analysis. Cancers. 2021;13(19):4816.

45. Dufresne A, Lindner LH, Striefler J, Kasper B, Van Houdt W, Litiere S, et al. The challenge of running trials in advanced angiosarcoma: A systematic review of the literature from EORTC/STBSG to guide the development of angiosarcoma-specific trials. European Journal of Cancer. 2024;207:114188.

46. Gupta RC, Lall R, Srivastava A. Efficacy, Safety, and Toxicity.

47. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nature reviews Clinical oncology. 2023;20(12):864-84.

48. Wu C, Yang P, Liu B, Tang Y. Is there a CDKN2A-centric network in pancreatic ductal adenocarcinoma? OncoTargets and therapy. 2020:2551-62.

49. Swanton C, Bernard E, Abbosh C, André F, Auwerx J, Balmain A, et al. Embracing cancer complexity: Hallmarks of systemic disease. Cell. 2024;187(7):1589-616.

ISSN: 3093-4737

50. Li A, Voleti R, Lee M, Gagoski D, Shah NH. High-throughput profiling of sequence recognition by tyrosine kinases and SH2 domains using bacterial peptide display. Elife. 2023;12:e82345.

51. Galipot P, Damerval C, Jabbour F. The seven ways eukaryotes produce repeated colour motifs on external tissues. Biological Reviews. 2021;96(4):1676-93.

52. Mas-Ponte D. Localized hypermutation and hypomutation in the genomes of human somatic cells. 2022.

53. Chen L, Liu S, Tao Y. Regulating tumor suppressor genes: post-translational modifications. Signal transduction and targeted therapy. 2020;5(1):90.

54. Aryankalayil MJ, Bylicky MA, Martello S, Chopra S, Sproull M, May JM, et al. Microarray analysis identifies coding and non-coding RNA markers of liver injury in whole body irradiated mice. Scientific reports. 2023;13(1):200.

55. Jia D, Jiang Z, Cui M, Ding X. Proteomics efforts for hepatocellular carcinoma drug development. Clinical Cancer Bulletin. 2024;3(1):22.

56. Patrad E, Khalighfard S, Amiriani T, Khori V, Alizadeh AM. Molecular mechanisms underlying the action of carcinogens in gastric cancer with a glimpse into targeted therapy. Cellular Oncology. 2022;45(6):1073-117.

57. Krasikova Y, Rechkunova N, Lavrik O. Nucleotide excision repair: from molecular defects to neurological abnormalities. International journal of molecular sciences. 2021;22(12):6220.

58. Shaverdian M. Immunothrombosis and Procoagulant Platelets in Feline Hypertrophic Cardiomyopathy: Uncovering Novel Activating Pathways and Therapeutic Targets: University of California, Davis; 2025.

59. Sadeesh N, Scaravilli M, Latonen L. Proteomic landscape of prostate cancer: The view provided by quantitative proteomics, integrative analyses, and protein interactomes. Cancers. 2021;13(19):4829.

60. Sorbini M, Carradori T, Togliatto GM, Vaisitti T, Deaglio S. Technical advances in circulating cell-free DNA detection and analysis for personalized medicine in patients' care. Biomolecules. 2024;14(4):498.

61. Hansen CE, Vacondio D, van der Molen L, Jüttner AA, Fung WK, Karsten M, et al. Endothelial-Ercc1 DNA repair deficiency provokes blood-brain barrier dysfunction. Cell Death & Disease. 2025;16(1):1.

62. Fang AHS, Lim WT, Balakrishnan T. Early warning score validation methodologies and performance metrics: a systematic review. BMC medical informatics and decision making. 2020;20(1):111.

63. Mora J, Palmer R, Wagner L, Wu B, Partridge M, Meena, et al. 2023 White Paper on Recent Issues in Bioanalysis: ISR for ADA Assays, the Rise of dPCR vs qPCR, International Reference Standards for Vaccine

ISSN: 3093-4737

Assays, Anti-AAV TAb Post-Dose Assessment, NanoString Validation, ELISpot as Gold Standard (Part 3–Recommendations on Gene Therapy, Cell Therapy, Vaccines Immunogenicity & Technologies; Biotherapeutics Immunogenicity & Risk Assessment; ADA/NAb Assay/Reporting Harmonization). Bioanalysis. 2024;16(7):77-119.

64. Ah-Pine F. Étude des mécanismes d'activation et de communication des cellules stromales mésenchymateuses en contexte pathologique chronique: Université de la Réunion; 2023.

65. Youvan DC. Epigenetic Insights into Human Diseases: Unraveling the Role of Gene Expression Modifications in Health and Disease. 2024.

66. Saulnier O, Guedri-Idjouadiene K, Aynaud M-M, Chakraborty A, Bruyr J, Pineau J, et al. ERG transcription factors have a splicing regulatory function involving RBFOX2 that is altered in the EWS-FLI1 oncogenic fusion. Nucleic Acids Research. 2021;49(9):5038-56.

67. Janic A, Abad E, Amelio I. Decoding p53 tumor suppression: a crosstalk between genomic stability and epigenetic control? Cell Death & Differentiation. 2025;32(1):1-8.

68. Sabatella M, Thijssen KL, Davó-Martínez C, Vermeulen W, Lans H. Tissue-specific DNA repair activity of ERCC-1/XPF-1. Cell reports. 2021;34(2).

69. Alcón P, Shakeel S, Chen ZA, Rappsilber J, Patel KJ, Passmore LA. FANCD2–FANCI is a clamp stabilized on DNA by monoubiquitination of FANCD2 during DNA repair. Nature structural & molecular biology. 2020;27(3):240-8.

70. Andrés-Sánchez N, Fisher D, Krasinska L. Physiological functions and roles in cancer of the proliferation marker Ki-67. Journal of cell science. 2022;135(11):jcs258932.

71. Aloke C, Onisuru OO, Achilonu I. Glutathione S-transferase: A versatile and dynamic enzyme. Biochemical and biophysical research communications. 2024;734:150774.

72. Farhat J, Alzyoud L, AlWahsh M, Acharjee A, Al-Omari B. Advancing Precision Medicine: The Role of Genetic Testing and Sequencing Technologies in Identifying Biological Markers for Rare Cancers. Cancer Medicine. 2025;14(8):e70853.

73. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024;187(7):1617-35.

74. Qureshi AA, Wehrle CJ, Ferreira-Gonzalez S, Jiao C, Hong H, Dadgar N, et al. Tumor organoids for primary liver cancers: A systematic review of current applications in diagnostics, disease modeling, and drug screening. JHEP Reports. 2024;6(12):101164.

75. Wu L, Wu Q, Du X, Ling M, Tong H. Revolutionizing pharmacological research of traditional Chinese medicine with single-cell omics technologies. Fitoterapia. 2025:106846.

ISSN: 3093-4737

76. Martinelli M. Identification of novel therapeutic strategies through newly developed in vivo Tumor models. 2024.

77. Colonna G. Unravelling the Barriers: Current Limitations in Cancer Biology Research and How to Overcome Them. 2025.

78. Skorupan N, Palestino Dominguez M, Ricci SL, Alewine C. Clinical strategies targeting the tumor microenvironment of pancreatic ductal adenocarcinoma. Cancers. 2022;14(17):4209.

79. Malchi T, Eyal S, Czosnek H, Shenker M, Chefetz B. Plant pharmacology: Insights into in-planta kinetic and dynamic processes of xenobiotics. Critical Reviews in Environmental Science and Technology. 2022;52(19):3525-46.

80. Philips CA, Rajesh S, Nair DC, Ahamed R, Abduljaleel JK, Augustine P, et al. Hepatocellular carcinoma in 2021: an exhaustive update. Cureus. 2021;13(11).

81. Sutherland RL. Biomarker-Guided Risk Prediction Models For The Presence Of High-Risk Polyps Among Screening-Eligible Populations In Alberta. 2025.

82. Pinto E, Pelizzaro F, Farinati F, Russo FP. Angiogenesis and hepatocellular carcinoma: from molecular mechanisms to systemic therapies. Medicina. 2023;59(6):1115.

83. Smith ZD, Hetzel S, Meissner A. DNA methylation in mammalian development and disease. Nature Reviews Genetics. 2025;26(1):7-30.

84. Yoshioka K-i, Kusumoto-Matsuo R, Matsuno Y, Ishiai M. Genomic instability and cancer risk associated with erroneous DNA repair. International journal of molecular sciences. 2021;22(22):12254.

85. Lodovichi S, Cervelli T, Pellicioli A, Galli A. Inhibition of DNA repair in cancer therapy: toward a multi-target approach. International Journal of Molecular Sciences. 2020;21(18):6684.

86. von Werdt A, Brandt L, Schärer OD, Rubin MA. PARP inhibition in prostate cancer with homologous recombination repair alterations. JCO Precision Oncology. 2021;5:1639-49.

87. Li J, Gong C, Zhou H, Liu J, Xia X, Ha W, et al. Kinase inhibitors and kinase-targeted cancer therapies: recent advances and future perspectives. International Journal of Molecular Sciences. 2024;25(10):5489.

88. Ababneh O, Nishizaki D, Kato S, Kurzrock R. Tumor necrosis factor superfamily signaling: life and death in cancer. Cancer and Metastasis Reviews. 2024;43(4):1137-63.

89. Morel D, Jeffery D, Aspeslagh S, Almouzni G, Postel-Vinay S. Combining epigenetic drugs with other therapies for solid tumours—past lessons and future promise. Nature Reviews Clinical Oncology. 2020;17(2):91-107.

90. Meraviglia-Crivelli D, Zheleva A, Barainka M, Moreno B, Villanueva H, Pastor F. Therapeutic strategies to enhance Tumor

ISSN: 3093-4737

Antigenicity: making the Tumor detectable by the Immune System. Biomedicines. 2022;10(8):1842.

91. Romualdo GR, Leroy K, Costa CJS, Prata GB, Vanderborght B, Da Silva TC, et al. In vivo and in vitro models of hepatocellular carcinoma: current strategies for translational modeling. Cancers. 2021;13(21):5583.

92. Berretta M, Dal Lago L, Tinazzi M, Ronchi A, La Rocca G, Montella L, et al. Evaluation of concomitant use of anticancer drugs and herbal products: from interactions to synergic activity. Cancers. 2022;14(21):5203.

93. Torrens Fontanals L. Molecular Characterization and Novel Therapeutic Approaches in Hepatocellular Carcinoma. 2022.

94. Fountzilas E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. Genome medicine. 2022;14(1):101.

95. Kremer D. Metabolic Regulation of Ferroptosis in Pancreatic Cancer 2020.

96. Kumar A, Metta D. AI-driven precision oncology: predictive biomarker discovery and personalized treatment optimization using genomic data. Int J Adv Res Publ Rev. 2024;1(3):21-38.

ISSN: 3093-4737

Mohammad, R. et al. (2026). **Uncovering Aristolochic Acid–Driven Mutational Signatures and Novel Biomarkers in Primary Hepatic Angiosarcoma for Targeted Therapeutic Development. Pan-African Journal of Health and Psychological Sciences. Vol. 2. No. 1. Jan-March 2026. https://doi.org/10.64261/55166d57.**